

**EXPRESS MAIL NO.: EV 250787254**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re US Patent No. 4,919,140:	Borgens, et al.
Filed	October 14, 1988
Issue Date	April 24, 1990
Title	Method And Apparatus For Regenerating Nerves
Attorney Docket No.	19232.0041

Mail Stop Hatch-Waxman PTE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

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SEP 29 2008  
PATENT EXTENSION  
OPLA

**TRANSMITTAL LETTER**

Dear Sir or Madame:

Transmitted herewith is an Application For Interim Patent Term Extension Under 35 U.S.C. §156(D) And 37 C.F.R. §1.710, Et Seq. for U.S. Patent No. 4,919,140 and supporting papers. Two copies of the Application For Interim Patent Term Extension Under 35 USC §156(d) And 37 CFR §1.710, Et Seq. are submitted as duplicate originals with Certifications. Also submitted herewith is a Change of Power of Attorney and Correspondence Address and Statement of Ownership .

The Commissioner is hereby authorized to charge the prescribed fee pursuant to 37 C.F.R. §1.20(j)(2) for the initial application for interim extension in the amount of \$420.00 fee to or credit overpayment to Deposit Account No. 09-0007 of Ice Miller, LLP.

1458

Respectfully submitted

A handwritten signature in black ink, appearing to read "David B. Quick", with a stylized flourish at the end.

David B. Quick, Reg. No 31,993  
Attorney for Applicant  
ICE MILLER LLP  
One American Square, #2900  
Indianapolis, IN 46282

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re US Patent No. 4,919,140:	Borgens, et al.
Filed	October 14, 1988
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**DECLARATION**

I, David B. Quick, an counsel attorney at Ice Miller LLP and an authorized patent attorney for Applicant, Purdue Research Foundation, submit this declaration, along with an Application for Interim Patent Term Extension Under 35 USC § 156(d) and 37 C.F.R. § 1.710, et seq. for U.S. Patent No. 4,919,140, and hereby state that:

(1) I am a patent attorney authorized to practice before the Patent and Trademark Office and have general authority from the owner to act on behalf of the owner in patent matters as demonstrated by the attached Power of Attorney or Revocation of Power of Attorney with a New Power of Attorney and Change of Correspondence Address and Statement Under 37 C.F.R. 3.73(b);

(2) I have reviewed and understand the contents of the application being submitted pursuant to 37 C.F.R. § 1.790;

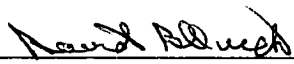
(3) I believe the patent is subject to extension pursuant to 37 C.F.R. § 1.790;

(4) I believe an interim extension of the length claimed is fully justified under 35 U.S.C. § 156 and the applicable regulations;

(5) I believe U.S. Patent No. 4,919,140 meets the conditions for an interim extension of the term of a patent as set forth in 37 C.F.R. § 1.790.

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Date: September 29, 2008

  
David B. Quick, Reg. No. 31,993  
Attorney/Agent for Applicant  
ICE MILLER LLP  
One American Square, #2900  
Indianapolis, IN 46282  
317-236-5972

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re US Patent No. 4,919,140:	Borgens, et al.
Filed	October 14, 1988
Issue Date	April 24, 1990
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**APPLICATION FOR INTERIM PATENT TERM EXTENSION**  
**UNDER 35 USC §156(d) AND 37 CFR §1.710, ET SEQ.**

Please find contained herein Purdue Research Foundation's application (the application and accompanying documents are collectively referred to herein as the "Application") for interim extension of United States Patent No. 4,919,140 under 35 U.S.C. §156(d)(5) and 37 C.F.R. §1.790. United States Patent No. 4,919,140 is owned by Purdue Research Foundation, 3000 Kent Avenue West Lafayette, Indiana 47906. Pursuant to 37 C.F.R. §1.710, et seq., the below information is provided. The paragraph numbers preceding each item correspond to the appropriate section of 37 C.F.R. §1.740(a) and in accordance to the mandate of 37 C.F.R. §1.790(b), Sections (a)(1), (a)(2), (a)(4) and (a)(6)-(a)17 of 37 C.F.R. §1.740 and 37 C.F.R. §1.741 are read in the

context of the product currently undergoing review, Section (a)(3) and (a)(5) not being applicable to the request for interim extension.

(1) A complete identification of the medical device currently undergoing review (hereinafter, the "Medical Device") which is intended to be made available under the trade name of Andara™ OFS™ System, including its physical structure or characteristics is attached as **Exhibit A** which includes pages taken directly from the documents submitted to obtain regulatory approval.

(2) The regulatory review occurred in three stages. In Stage I clinical trials were conducted in compliance with IDE regulations in 21 CFR part 812, institutional review board regulations in 21 CFR part 56, and the informed consent regulations in 21 CFR part 50 pursuant to an IRB. In Stage II, the regulatory review comprised an Investigational Device Exemption Number Request under the Federal Food Drug and Cosmetic Act Section 520(g) (21 U.S.C. §360j(g)). In stage III, the regulatory review comprised a request for an Humanitarian Device Exemption under Investigational Device Exemption Number Request under the Federal Food Drug and Cosmetic Act Section 520(m) (21 U.S.C. §360j(m)).

(3) Not applicable to interim extension.

(4) Not applicable to requests for extension for medical devices.

(5) Not applicable to interim extension, however this application is being filed within the window of six months prior to the expiration of the term of the patent and fifteen days prior to the expiration of the term of the patent as prescribed in 35 U.S.C. §156(d)(5)(A). The patent term is to expire October 14, 2008, with the last day on which the Application for filing the interim extension request falling on September 30, 2008.

(6) This Application is for United States Patent No. 4,919,140 (the "OFS Patent"). The subject matter of the OFS Patent was invented by Richard B. Borgens and Michael E. McGinnis. The OFS patent was assigned to Purdue Research Foundation by an assignment executed December 9, 1988 and recorded on December 15, 1988 with the United States Patent and Trademark Office at reel 004992, frame 0592. The OFS Patent was filed October 14, 1988 and issued April 24, 1990. Pursuant, to 35 U.S.C. §154 the OFS Patent, upon payment of maintenance fees, is entitled to a term which is the greater of seventeen years from the issue date (April 24, 2007) or twenty years from the filing date (October 14, 2008). Thus, the date of expiration of the OFS Patent is October 14, 2008.

(7) A copy of the OFS Patent, including the specification (including claims) and drawings is attached as **Exhibit B**.

(8) Maintenance fees were paid on this patent on October 26, 1993, October 24, 1997 and October 25, 2001 to maintain the term of the patent until October 14, 2008. A copy of the receipt for the maintenance fees for the OFS Patent is attached as **Exhibit C**. No disclaimer, certificate of correction or reexamination certificate applies to the OFS Patent.

(9) The OFS Patent claims the Medical Device. A demonstration of the manner in which at least one such patent claim reads on the Medical Device and the method of use is attached as **Exhibit D**.

(10) Pursuant to 37 C.F.R. §1.740(a)(10)(v), a statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g) is attached as **Exhibit E**.

(11) A brief description of the significant activities undertaken by Purdue Research Foundation, its licensees Depuy, Andara Life Sciences, Inc. and Cyberkinetics Neurological Systems, Inc. and their Sponsors of studies during the applicable regulatory period with respect to the Medical Device and the significant dates applicable to such activities is attached as **Exhibit F**.

(12) A statement that in the opinion of the Applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined is attached as **Exhibit G**.

(13) Purdue Research Foundation acknowledges its duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought, and the tenets of the duty of disclosure in 37 C.F.R. §1.765 relevant to the application.

(14) The Commissioner is hereby authorized to charge the prescribed fee pursuant to 37 C.F.R. §1.20(j)(2) or any additional fee, or credit overpayment, to Deposit Account No. 09-0007 of Ice Miller LLP.

(15) Any inquiries and correspondence relating to this application should be directed to:


David B. Quick  
ICE MILLER LLP  
One American Square  
Suite 2900  
Indianapolis, IN 46282-0200

Purdue Research Foundation is asking for an interim extension of U.S. Patent No. 4,919,140 until the earlier sixty days following Regulatory Approval of the Medical



Device or October 14, 2009. If there is any questions on this application, please contact the agent for the applicant, as noted above. Signatory below is authorized to sign this Application on behalf of Purdue Research Foundation pursuant to a Power of Attorney or Revocation of Power of Attorney and Change of Correspondence Address accompanied by a Statement Under 37 C.F.R. 3.73(b) signed by an authorized agent of Purdue Research Foundation.

Respectfully Submitted



David B. Quick, Reg. No. 31,993  
Attorney for Applicant  
ICE MILLER LLP  
One American Square  
Suite 2900  
Indianapolis, IN 46282-0200

DBQ/sg

Encl: Exhibits A-G  
Appendix A-F  
POA & Statement Under 37 CFR 3.73(b)  
Declaration  
Certification  
Transmittal Letter  
Return Postcard



PTO/SB/81 (07-08)

Approved for use through 12/31/2008. OMB 0651-0035

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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**POWER OF ATTORNEY  
OR  
REVOCATION OF POWER OF ATTORNEY  
WITH A NEW POWER OF ATTORNEY  
AND  
CHANGE OF CORRESPONDENCE ADDRESS**

Application Number	07/268,142 Pat. No. 4,919,140
Filing Date	October 14, 1988
First Named Inventor	BORGES
Title	Method and Apparatus for Regenerating Nerves
Art Unit	3305
Examiner Name	MANUEL, George C.
Attorney Docket Number	P01732-US-00 (if/ta 3220-18158)

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

22446

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☐ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☒ Firm or Individual Name David B. Quick ICE MILLER LLP

Address One American Square, Suite 2900

City Indianapolis State IN Zip 46282

Country USA

Telephone 317-236-5972 Email david.quick@icemiller.com

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on \_\_\_\_\_

**SIGNATURE of Applicant or Assignee of Record**

Signature	<i>Judith A. Hall</i>	Date	September 29, 2008
Name	Judith A. Hall	Telephone	765-494-2610
Title and Company	Corporate Secretary		

**NOTE:** Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below\*.☐ \*Total of \_\_\_\_\_ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**STATEMENT UNDER 37 CFR 3.73(b)**Applicant/Patent Owner: Purdue Research FoundationApplication No./Patent No.: 4,919,140Filed/Issue Date: 10/14/88 4/24/90Entitled: METHOD AND APPARATUS FOR REGENERATING NERVES

Purdue Research Foundation

(Name of Assignee)

, a

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest  
(The extent (by percentage) of its ownership interest is \_\_\_\_\_ %)

in the patent application/patent identified above by virtue of either:

- A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 004992, Frame 0592, or for which a copy therefore is attached.

OR

- B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at

Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

2. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at

Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

3. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at

Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

- ☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Judith A. Hall

Signature

September 29, 2008

Date

Judith A. Hall

Printed or Typed Name

765-494-2610

Telephone Number

Corporate Secretary

Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/SB/81 (07-08)

Approved for use through 12/31/2008. OMB 0651-0035

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<b>POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS</b>	<b>Application Number</b>	07/258,142 Pat. No. 4,919,140
	<b>Filing Date</b>	October 14, 1988
	<b>First Named Inventor</b>	BORGES
	<b>Title</b>	Method and Apparatus for Regenerating Nerves
	<b>Art Unit</b>	3305
	<b>Examiner Name</b>	MANUEL, George C.
	<b>Attorney Docket Number</b>	P01732-US-00 (t/k/a 3220-18158)

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

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Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☐ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☒ **Firm or Individual Name** David B. Quick ICE MILLER LLP**Address** One American Square, Suite 2900**City** Indianapolis **State** IN **Zip** 46282**Country** USA**Telephone** 317-236-5972 **Email** david.quick@icemiller.com

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.

Statement under 37 CFR 3.73(b) (Form PTO/SB/98) submitted herewith or filed on \_\_\_\_\_

**SIGNATURE of Applicant or Assignee of Record**

<b>Signature</b>	<i>Judith A. Hall</i>	<b>Date</b>	September 29, 2008
<b>Name</b>	Judith A. Hall	<b>Telephone</b>	765-494-2610
<b>Title and Company</b>	Corporate Secretary		

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Applicant/Patent Owner: Purdue Research Foundation

Application No./Patent No.: 4,919,140

Filed/Issue Date: 10/14/88

4/24/90

Entitled: METHOD AND APPARATUS FOR REGENERATING NERVES

Purdue Research Foundation, a

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

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2. ☐ an assignee of less than the entire right, title and interest  
(The extent (by percentage) of its ownership interest is \_\_\_\_\_ %)

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OR

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3. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
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☐ Additional documents in the chain of title are listed on a supplemental sheet.

- ☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Judith A. Hall  
Signature

September 29, 2008  
Date

Judith A. Hall

Printed or Typed Name

765-494-2610

Telephone Number

Corporate Secretary

Title



# **Andara™ OFS™ System**

*for the Treatment of Acute, Complete Spinal Cord Injury*

## ***DEVICE DESCRIPTION***

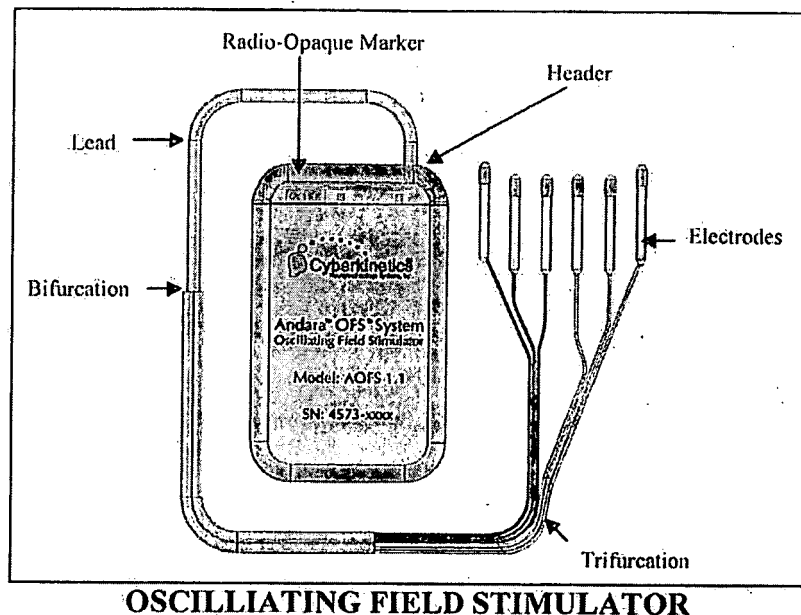
**Cyberkinetics Neurotechnology Systems, Inc.**

100 Foxborough Blvd, Suite 240  
Foxborough, MA 02035

**EXHIBIT A**

## I. DEVICE DESCRIPTION

The Andara OFS System is comprised of three components: 1) the Oscillating Field Stimulator, 2) the Beacon Receiver, and 3) the Lead Cap. The Oscillating Field Stimulator and the Lead Cap are supplied sterile.



**OSCILLATING FIELD STIMULATOR**

### OSCILLATING FIELD STIMULATOR

The Oscillating Field Stimulator weighs 70 grams and is 40cc +/-10% in size. The electronics are housed in a hermetically sealed titanium can with a header from which two leads emanate. The two leads exit the header as a single, silicone insulated wire bundle. This wire bundle then bifurcates into two separate insulated wires, each of which subsequently trifurcates into three separate insulated wires with an electrode at the end of each wire; resulting in a total of six electrodes. The electrodes are provided in two bundles of three electrodes, with one bundle containing white electrodes and the other bundle containing black electrodes. During implantation, the electrodes are oriented such that one color of bundled electrodes is placed above the site of injury and the other color of bundled electrodes is placed below the site of

**EXHIBIT A-2**

injury (it does not matter which color bundle is placed above or below the site of injury). The circuitry of the Oscillating Field Stimulator is designed such that each bundle of three electrodes has an opposite charge. When one bundle is positive, the other bundle is negative, and vice-versa. The circuitry is designed to oscillate every 15 minutes. The Oscillating Field Stimulator produces an output of approximately 600  $\mu\text{A}$  to achieve an electrical field in the target tissue of approximately 600  $\mu\text{V}/\text{mm}$ . The current is distributed between three electrodes, providing approximately 200  $\mu\text{A}$  per electrode.

When implanted there are four materials which come into contact with body tissue. All four materials are widely used in implantable devices and are biocompatible. The materials are titanium (can), epoxy (header), Silicone (leads), PTFE (leads) and Platinum iridium (lead tip).



**BEACON RECEIVER**

## **BEACON RECEIVER**

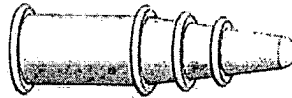
The Beacon Receiver is an accessory which can be used by a physician or healthcare professional to confirm the Oscillating Field Stimulator is turned on. The Beacon

**EXHIBIT A-3**

CONFIDENTIAL



Receiver may be used in the Operating Room at the time of implantation of the Oscillating Field Stimulator or at anytime during the course of the 15 week therapy.



**LEAD CAP**

### **LEAD CAP**

The Lead Cap is a small silicone cap which is placed over the end of a cut lead if a physician is unable to remove a lead from the patient at the time the Oscillating Field Stimulator is explanted.

**EXHIBIT A-4**

## II. COMPARISON OF CLINICAL TRIAL DEVICE TO THE CURRENT CONFIGURATION

Cyberkinetics Neurotechnology Systems, Inc. has elected to take advantage of advances in technology and manufacturing to update the device used in the clinical trial to a more state-of-the-art configuration. The new, current configuration is functionally identical to the device that was used in the clinical trial. The following is a table which details the differences between the two configurations and the rationale for the change.

Key Element	Clinical Trial Device	Current Configuration	Rationale for Change
Electronic Components	Circuitry board controls DC current, reversal of current polarity, fail-safe circuit, and beacon	Same	N/A
Power Source	One 3.6V organic lithium battery (Tadiran TL 5903/T)	Two 2.8V lithium carbon monofluoride battery in series (WGL 9086) with voltage regulator to provide output of 3.6 volts	Implantable grade battery with proven manufacturing history
Leads	Three pair of PTFE-insulated electrical leads	Three pair of PTFE-insulated electrical leads	N/A
Electrodes	Six lead tips Pt(90%) / Ir(10%) coils	Same	N/A
Output per Lead	200 microAmps	Same	N/A
Field Strength	500-600 microVolts/mm	Same	N/A
Casing	Cylindrical, transparent Teflon® jacket, sealed at both ends with silicone elastomer	Hermetically sealed titanium can with silicone/epoxy header	Repeatable and reliable manufacturing process, physiologic shape
Volume	Less than 25 cc	Less than 40 cc	Increased to allow for batteries (see above)
Weight	About 37 grams	About 70 grams	Increased to allow for batteries (see above)

### EXHIBIT A-5

## PRINCIPLES OF OPERATION

The Andara OFS System consists of three components; an implantable stimulator designed to apply an alternating electrical stimulation between two sets of three electrodes, a non-implantable beacon receiver with antenna designed to receive a beacon signal from the implantable indicating the implantable is functioning, and a lead cap designed to be placed over the end of a cut lead in the event that the surgeon is not able to remove the lead.

### **Implantable Stimulator**

The function of the implantable device is to stimulate the re-growth of damaged nerve fibers at the site of a severely damaged spinal cord.

The implantable device is intended to be implanted in the body for 15 weeks. The lead sets are placed in the body with three leads of the same polarity placed above the damaged site and three leads placed below the damaged site.

A reed switch and magnet are used to hold the device in an off state once the battery is connected to the electronic circuits. The implantable device is supplied in sterile packaging with a magnet positioned in the packaging to keep the device in an off state. Once the device is removed from the packaging, the OFS becomes active. When on, the OFS device will produce an alternating current of 200  $\mu$ A in each of the six implanted electrodes. Current flows from one set of three electrodes to the opposite set and changes polarity at a fifteen minute interval. While on, the OFS device will periodically transmit a beacon signal to provide confirmation the device is functioning.

The implantable is powered by two WGL 9086 batteries. Each battery provides a capacity of 2500 mA/hrs at 2.8 volts and can provide a sustained total current draw in excess of 700  $\mu$ A for the 15 week implant period. The two cells are connected in series to provide a voltage of approximately 5.6 volts which is regulated to the OFS functional voltage of 3.6 volts. The voltage regulator device also has a comparator circuit that is used in conjunction with the TPS3823-33 watchdog chip to assert the RESET signal when the regulated output falls under the selected end of life 3.0 volt limit as will happen when the batteries deplete. The RESET signal is used to shut down the switching function of the device and place the outputs in a tri-state (non current flow) condition.

The 3.0 volt end of life limit is chosen to meet the minimum operating voltage requirements of the electronic components with an appropriate safety margin.

A 4060 binary ripple counter with mono-stable multivibrator provides the timing controller for therapy switching. The 14<sup>th</sup> stage output of the ripple counter is used to drive the therapy switching at a rate of once every 15 minutes. The six electrodes are grouped into two sets of three lead pairs. Therapy current alternates between these two groups of three electrodes. LM 334M current regulators are used to provide a 200uA current across the each of the three lead pairs for a total therapy current of 600uA.

The 6<sup>th</sup> stage output from the counter is also used to activate the beacon signal oscillator circuit. The implantable periodically sends a burst signal of approximately 70 KHz with a burst duration of 20 milliseconds every seven seconds. The burst is intended to provide remote evidence the implantable is functioning properly.

The Andara OFS implantable contains a failsafe circuit utilizing the Texas Instruments TPS3823-33 device as was used in the IDE device design. The failsafe circuit provides the reset and protection functions. If the regulated voltage is less than 3.0 volts maximum the /RESET is asserted. If the oscillator-timer chip stops the watchdog input stops and the TPS3823-33 asserts /RESET. Therapy current delivery is stopped when the /RESET line is asserted.

Lead construction follows typical pacemaker technology with a standard DBS 7X7 cable conductor and a PTFE coating. Silicone tubing is used to bundle the six lead cables in the proximal length of the leads and to electrically isolate the conductor to electrode wire joint.

#### **Beacon Receiver**

The Beacon Receiver consists of an antenna module connected by a fixed shielded cable to a handheld enclosure containing the receiver circuitry. The antenna is a wound coil of wire approximately 2.0 inches in diameter. The antenna may be sterile bagged to allow for use in the sterile field during the implant procedure.

The antenna signal is lowpass filtered and amplified by an instrumentation amplifier. The signal is then bandpass filtered by an active operational amplifier infinite-gain multiple-feedback circuit. The signal is then amplified and bandpass filtered again. Next

the peak-to-peak signal is rectified and filtered. When the filtered rectified signal reaches a 0.6 volt threshold level a comparator outputs a high logic level signal. When the comparator output goes low after the strength of the input signal diminishes two monostable multivibrators are triggered. One of the multivibrators has an output period of one second. The multivibrator's /Q output drives a P-Channel MOSFET high side switch that activates a buzzer. The multivibrator's Q output drives a N-Channel MOSFET low side switch that activates the OFS ACTIVE LED. The other monostable multivibrator has a period of five seconds and prevents retriggering to limit nuisance false indication.

The Beacon Receiver is powered by two PP3 9-Volt batteries. Current limiting PTC thermistors are used to limit power dissipation in the event of a short circuit failure. Reverse polarity protection diodes protect the Beacon Receiver electronics in the event that a battery is installed incorrectly.

A power switch is used to turn the device 'on' and 'off'. An LED is used to provide a visual power indication.

### **Lead Cap**

The lead cap is an accessory that may be used during the surgical procedure in which the generator is explanted after completion of the 15 week course of therapy. The lead cap is only used in cases in which the surgeon is not able to remove the lead itself. In these cases, the lead cap is placed over the exposed wire of the cut lead and sutured into place.

## Implantable BOM for Genesis device

1	Shrink Tubing	6
2	Shrink Tubing	6
3	Epoxy Clear 2 Part	
4	Bracket, Anchor, .015" Formed Ti	2
5	Battery Terminal Config WGL 9086	2
6	Adhesive, Silicone Nusil MED-1137	
7	Crimp Sleeve, Feedthrough	6
8	Crimp Sleeve, Electrode	6
9	Cable, Insulated (Clear)	3.63
10	Cable, Insulated (Black)	3.63
11	Wire, 90/10 Pt-Ir, 0.007" dia.	4.00
12	Final Can Assembly	1
13	Silicone Tubing (0.092" dia. OD)	0.44
14	Silicone Tubing (0.084" dia. ID)	0.42
15	Silicone Tubing (0.063" dia. ID)	0.67
16	Feedthrough Assy, Tri-Polar	2
17	Machined Lid	1
18	Copper Wire	2
19	PCB Spacer	2
20	Header Mold	1
21	Outer Tray	1
22	Inner Tray	1
23	Outer Tray Lid	1
24	Inner Tray Lid	1
25	Bottom Nest	1
26	Top Nest	1
27	Nest Spacer	2
28	PCB Genesis Timer Board	1
29	PCB Genesis Current Board	1
30	X-Ray Tag	1
31	Magnet	1
32	Shelf Box	1
33	IFU	1
34	Feedthrough Wire (set-up)	N/A
35	Lead Cap	6

Item	Description	Qty
1	Genesis Timer Board Schematic	0
2	VOLT REG 16Vin 5Vout 300mA 2% 960mW +5 V Fixed or Adjustable Low-Dropout Linear Voltage Regulator w/SHDN w/LBO, SOIC-8	1
3	CAP 0805 1.0uF 10V +10%/-10% ceramic	1
4	CAP Size A 4.7uF 10V +10%/-10% Solid Tantalum Chip 3216-18 EIA Size	1
5	CAP 1206 10uF 6.3V +20%/-20% Multilayer Ceramic	1
6	CAP 0603 .1uF 16V +10%/-10% X7R	1
7	CAP 0603 .047uF 16V +10%/-10% ceramic X7R	4
8	INDUCT 1812 220uH 0.1A +-10% Tolerance, Q 40, DCR Max 10 Ohms, -55 Deg C to +125 Deg C	1
9	TRANS NPN SOT-23 MMBT3904	1
13	RES 0603 1Kohm 0.1W ±1% Metal Glazed Thick Film Chip Resistor	1
14	RES 0603 1Mohm 0.062W ±1% Metal Glazed Thick Film Chip Resistor	4
16	RES 0603 10Kohm 0.1W ±1% Metal Glazed Thick Film Chip Resistor	1
17	RES 0603 20Kohm 0.1W ±1%	1
18	IC Single Inverter Gate SOT-553 2V to 5.5V Operation, -40 Deg C to +85 Deg C, AHC Logic Family	2
19	IC Single Bus Buffer Gate w/3-State Output SOT-553 2V to 5.5V Operation, -40 Deg C to +85 Deg C, AHC Logic Family	3
20	IC 14-Stage Ripple Carry Binary Counter and Oscillator 16-TSSOP 3V to 18V Operation, -55 Deg C to +125 Deg C	1
21	IC Single Inverter Buffer/Driver w/ Open-Drain Output SOT-553 1.65V to 5.5V Operation, -40 Deg C to +85 Deg C	1
22	SWITCH, REED, SMT, 10 mA max, .042 tall X .050 wide X .240 long maximum, -40 Deg C to +125 Deg C	1
23	IC Processor Supervisory Circuits, 3.3V (2.93 V Threshold) SOT23-5 200 ms POR, Manual Reset Input, Active Low Reset Output, Watchdog Timer, -40 Deg C to +125 Deg C	1
25	RES 0603 316Kohm 0.062W ±1% Thick Film Chip Resistor	1

26	RES 0603 10Mohm 0.1W $\pm 5\%$	1
27	RES 0603 22Mohm 0.1W $\pm 10\%$ Thick Film Chip Resistor	1
28	RES 0603 42.2Kohm 0.1W $\pm 1\%$ Thick Film Chip Resistor	1
29	PCB Genesis Timer Board	1
30	ASBY Drawing for Genesis Timer Board	0
31	RES 0603 348Kohm 0.1W $\pm 1\%$ Thick Film Chip Resistor	0
32	RES 0603 191Kohm 0.1W $\pm 1\%$ Thick Film Chip Resistor	1



<i>Item</i>	<i>Description</i>	<i>Qty</i>
1	Genesis Current Board Schematic	1
2	RES:0603 348ohm 0.1W ±1% Thick Film Chip Resistor	12
3	IC Current Source SOIC-8 Resistor Programmed	12
5	PCB: Genesis Current Board	1
6	ASBY Drawing for Genesis Current Board	0
7	RES:0603 348ohm 0.1W ±1% Thick Film Chip Resistor	0

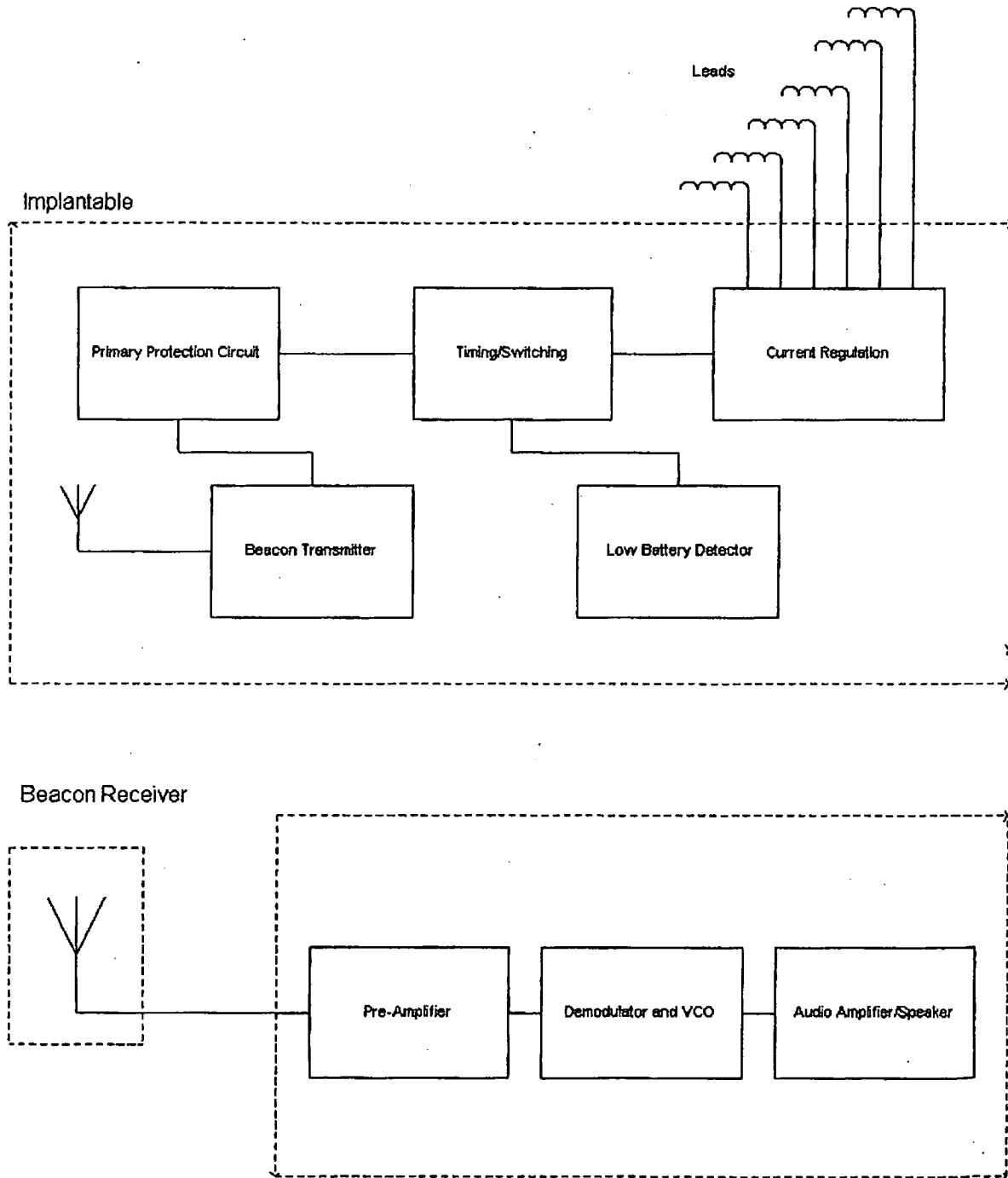
EXHIBIT A-12

### 3 FMECA Diagrams

The below diagram(s) are used to perform the failure analysis.

#### 3.1 System Block Diagram

Andara OFS System Block Diagram



## 1 INTRODUCTION AND SCOPE

The Andara™ OFST™ (Oscillating Field Stimulator) System is intended for the treatment of acute, complete spinal cord injury (SCI). This document defines the product requirements for the Andara™ OFST™ System. The system consists of an oscillating field stimulator (also referred to as “generator,” “implant,” or “device”), a beacon receiver and lead caps.

The oscillating field stimulator consists of an implantable generator and 3 pair of leads with one electrode at the distal end of each lead. The device provides approximately 600  $\mu\text{V}/\text{mm}$  oscillating electrical field allocated among 3 electrode pairs. Three electrodes are placed two vertebral segments rostral and three electrodes are placed two vertebral segments caudal to the site of the spinal cord injury. The oscillating field stimulator is designed to provide a low voltage electrical field with the polarity of the field reversing every 15 minutes between the paired electrodes. The oscillating electrical field has been shown to regenerate nerve tissue at the site of injury. The oscillating field stimulator is designed to be implanted within 18 days of a spinal cord injury for 15 weeks. This device will be qualified as chronic medical implant.

The beacon receiver is an accessory that provides confirmation that the oscillating field stimulator is turned on and functioning. The beacon receiver is designed to be used during the surgical procedure in which the oscillating field stimulator is implanted in the patient and also throughout the 15 week course of therapy.

The lead cap is an accessory that may be used during the surgical procedure in which the generator is explanted after completion of the 15 week course of therapy. The lead cap is only used in cases in which the surgeon is not able to remove the lead itself. In these cases, the lead cap is placed over the exposed wire of the cut lead and sutured into place.

The Andara™ OFST™ System is currently being implanted in a feasibility study (IDE # G000195/S6). Cyberkinetics is pursuing Humanitarian Device Exemption (HDE) status from the FDA. If approved for HDE we anticipate a potential market of 3500 patients per year in the U.S. and four times that number worldwide.

The Andara™ OFST™ project will be conducted in accordance with applicable FDA and European requirements for an Active Implantable Medical Device (AIMD).

### EXHIBIT A-14

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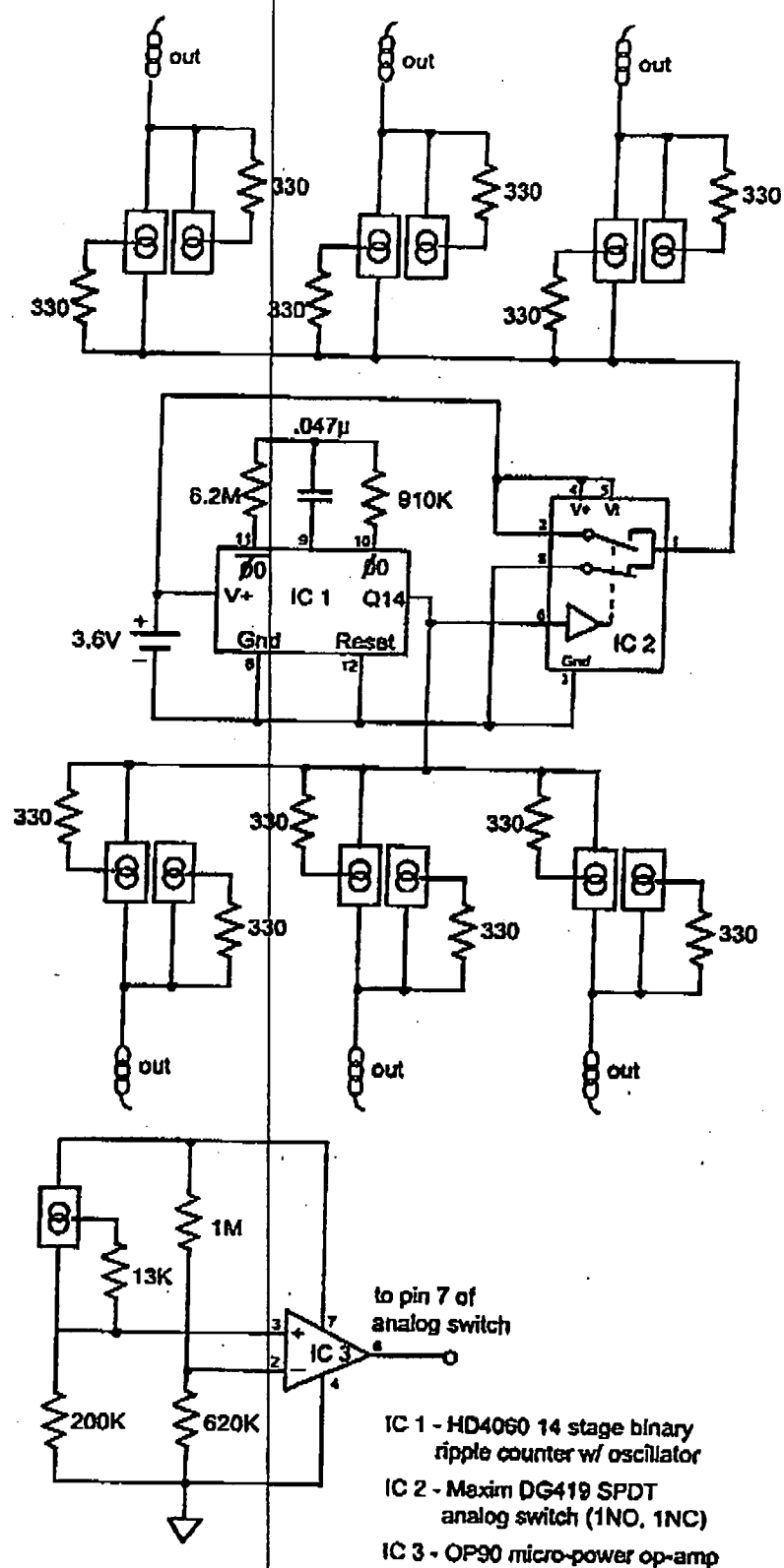


Fig. 1, Borgens et al., J. Neurotrauma

EXHIBIT A-15

appreciation, ambulation, and proprioceptive placing of the hindfeet ) - *none of the sham treated animals did.*

4) The combined neurological score was significantly different between these groups at 8 weeks ( $p < 0.033$ ) and at the 6 month ( $p < 0.035$ ) recheck period<sup>52</sup>.

In summary OFS stimulation appears to be an effective technique to facilitate recovery of function in clinical cases of spinal trauma if applied within 1 month of the injury. Due to the lack of a proper control group for long term chronically injured animals, investigators were unable to demonstrate any statistically significant response to treatment when the application was made at greater times post injury though there were trends in recovery in this group as well<sup>52</sup>.

#### OFS units for human phase one trials

The " human use OFS unit is distinct from that previously described :

1. The effective field strength is trippled by using symetrical arrays of electrodes ( 3 pair ) - each delivering the same current denslty as used previously and found safe in canine clinical trials.

Since the measured field strength in spinal cord parenchyma correlates more with the cross-sectional area of the animal than with electrode placement<sup>21</sup>, tripling the total current over that previously used produces a similar field strength at the spinal cord lesion in humans as found effective in paraplegic dogs<sup>52</sup> ( Humans average a three fold greater cross sectional area than that of canines used in these veterinary clinical trials).

2. \* Fail safe circuitry has been incorporated into the circuit so that unit shutdown occurs when non nominal operation might occur.

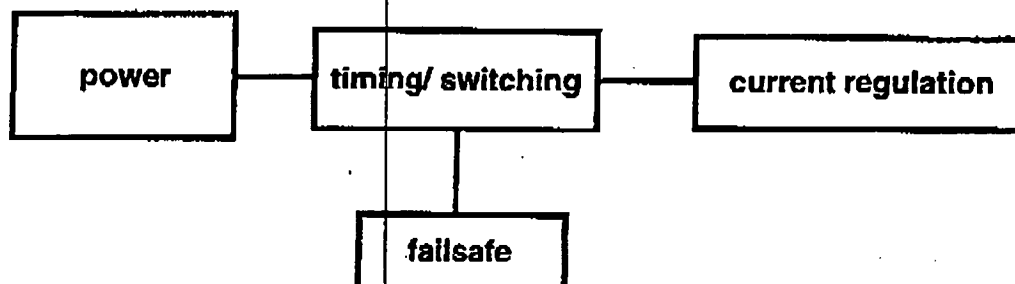
3. More durable platinumun / indium electrodes fused to insulated surgical stainless multistrand wire ( pacemaker pacer cables ) are now employed.

4. OFS units operate continuously for about 16 weeks untill the voltage source is exhausted.

These units have been recently used in a three year long blinded trial in canine paraplegia and functioned without problem. Unacceptable clinical symptoms, indeed any type of clinical complication, did not arise during the 3 years of clinical observation.

### **OFS Stimulator Design**

Details of the construction of a circuit that provides regulated current output from multiple electrodes and oscillates the polarity of the applied electric field at a predetermined time has been previously provided <sup>19,52</sup>. As discussed above, These constructions have been completely redesigned to produce a new generation of OFS stimulators that: 1) produce a ca. three fold increase in current (~500-600 uA total current) over those used previously (at most delivering 200 uA total current; based on in situ quadrapole measurements <sup>52</sup>), 2) use three pairs of electrodes whose circuits are independently regulated but timed to invert their polarity in synchrony, 3) contain an external switch that can be activated easily permitting a shelf life for units on the order of years. This allows the units to be stored for use without battery drain, and activated at any time and 4) contain "fail-safe" circuitry which terminates functioning at non-nominal operation, particularly a failure in oscillation. Given this design has not been reported elsewhere, and will be used in phase one human clinical testing, we provide full details of its construction and operation.

Block diagram of OFS and Circuit Operation

The OFS stimulators consisted of main circuitry sections, or blocks. The power block provided the DC power source for the unit. A single 3.6 volt organic lithium battery (Tadiran TL 5903/T) with a rated capacity of 2400 mA/H was chosen as the power source because of this high capacity, and its size and shape. The second block provided the timing and polarity reversal functions of "oscillation." Its main timing component was a 4060 14-stage binary ripple counter with an onboard oscillator (refer to the circuit schematic, Fig 1, for the following description). The timing was set with a Resistance/Capacitance network and the output taken from the 14th stage (Q14) for the maximum period. The output (Q14, or the last stage of the 14 timing stages) acted as a reference that changed every 15 minutes. The output from Q14 served two functions: 1) it drove one half of the current regulation circuit, and 2) it triggered an analog switch which, in turn, drove the other half of the current regulation circuit. The 4060 is a low-power complimentary metal oxide semiconductor (CMOS) device and consumed only a few microamps.

The complimentary component of the timing/switching block was a Maxim DG319 single pole double throw (SPDT) analog switch. It used the Vcc (or power connector) and ground as inputs and was switched between these by the

output of the oscillator timing action of the Q14. It was arranged such that the output of the switch was always the complement of Q14, and was therefore used to drive the other half of the current regulation circuit. The DG319 was also a low-power CMOS device and consumed only a few microamps.

The analog switch operates nominally to a voltage of 2.5 volts. At that point, switching action stops and the output is locked in a non-oscillating state. The oscillator fail-safe utilized a Maxim 921, which is a single integrated semiconductor chip containing a comparator and a 1.2 volt reference. A voltage divider set the threshold voltage of the comparator to 2.6 volts and the output was connected to the VI input of the analog switch. When the power to the circuit falls to 2.6 volts, the output from the comparator changes from low to high and shorts out the analog switch. This short circuits the power to the entire circuit which subsequently shuts down all output to the electrodes.

The current regulation block of the OFS was based upon the LM334Z constant current source. The 334 is a stand-alone 3 terminal semiconductor device whose current output was programmed by a single resistor. That output was maintained until the resistance of the load exceeded the compliance of the voltage source or the voltage source fell below the operating voltage of the LM 334Z (ca. 1.8 V). The circuit had 2 arrays of 334s (one on each side) that fed the three sets of electrodes. Each pair delivered 200 $\mu$ A, producing a total current of 600 $\mu$ A (associated with a field of ca. 500-600  $\mu$ V/mm given the standard array of electrodes used here ). As seen in Fig. 1, the 334s were arranged in a "piggy back" fashion on both sides of the arrays. This was to provide accurate source/sink conditions for current delivery. This insured that the 600 $\mu$ A is distributed evenly across the lead pairs, none of them delivered



more or less current than the others in polarized synchrony. The set resistors of the 334s were integrated into dual inline packages (DIP) to keep the unit organized and modular. The output leads were made of silicone rubber insulated stainless steel to minimize wire corrosion in the case of leakage around the electrode solder joint or a breach in the leads' insulation. The uninsulated stimulating electrodes were a Platinum/Iridium (PtIr) alloy. 20 cm lengths of the PtIr wire were tightly coiled in order to increase the surface area of current delivery further minimizing current density at the electrodes.

The overall circuit is provided in Fig.1 and a radiograph of the new design OFS unit in situ is provided in Fig 2. The hand fabricated circuit was inserted into a hollow teflon cylinder and the electronic components and voltage source perfused and sealed within the cylinder with epoxy. The end of the cylinder plus the electronic circuit was sealed with medical grade elastomer. The six electrodes exiting the other end of the teflon cylinder were also sealed with medical grade elastomer. The two sets of three electrodes were insulated with two different colors for correct implantation by the surgeon to insure that polarity reversal for each set was symmetrical—one set of three electrodes being located rostral to the injury site, the other set caudal to it.

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[54] METHOD AND APPARATUS FOR REGENERATING NERVES

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[73] Assignee: Purdue Research Foundation, West Lafayette, Ind.

[21] Appl. No.: 258,142

[22] Filed: Oct. 14, 1988

[51] Int. Cl.: A61N 1/00

[52] U.S. Cl.: 128/422; 128/421; 128/419 R; 128/784

[58] Field of Search: 128/421, 422, 419 F, 128/419 R, 783, 784

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Primary Examiner—Francis Jaworski

Assistant Examiner—George Manuel

Attorney, Agent, or Firm—Barnes & Thornburg

[57]

ABSTRACT

A method and apparatus for stimulating nerves in the central nervous system of a mammal to regenerate within the central nervous system applies an oscillating electrical field to the central nervous system across a lesion in the central nervous system. The polarity reversal period of the electrical field is long enough to stimulate growth of cathodally facing axons of the nerve cells in the central nervous system but is shorter than a die back period of anodally facing axons of the nerve cells.

11 Claims, 2 Drawing Sheets

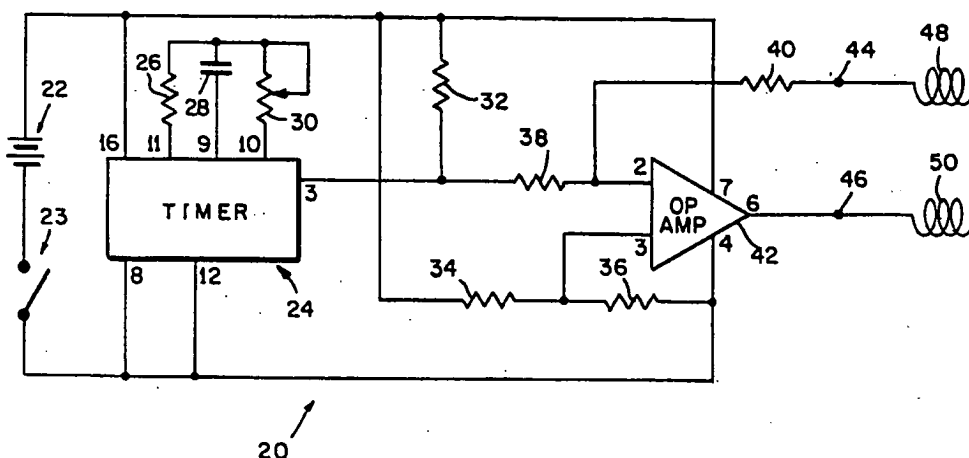
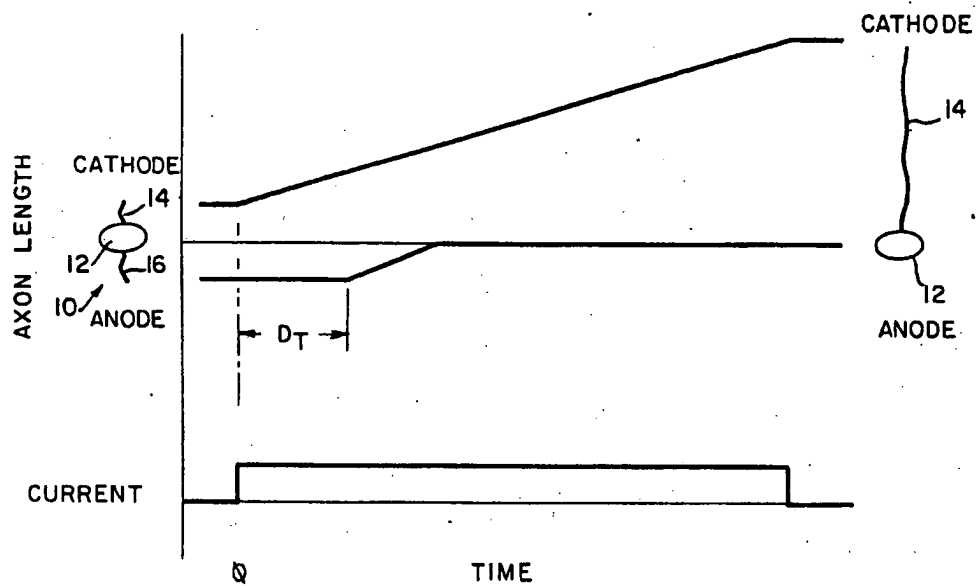
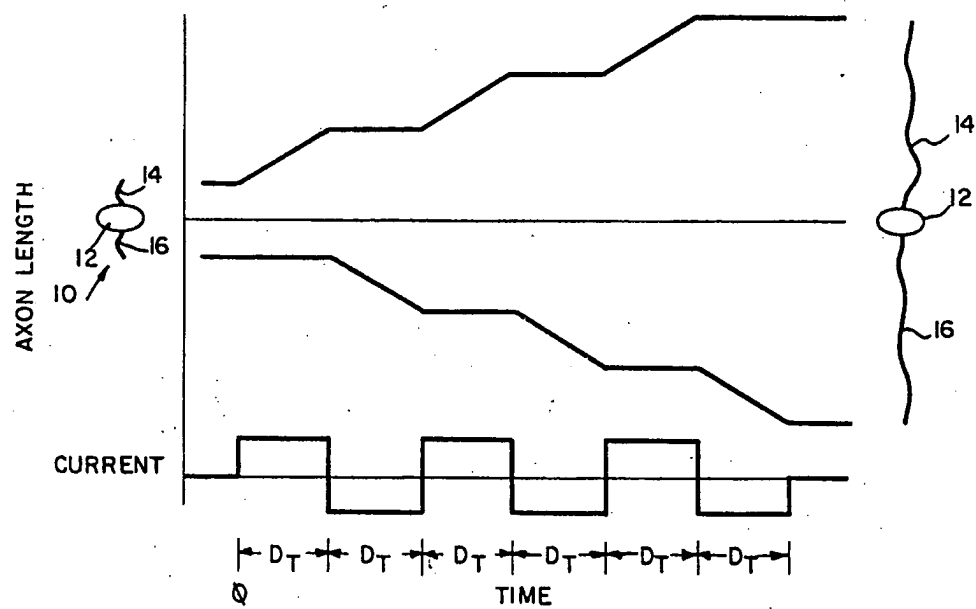


EXHIBIT B

*FIG. 1**FIG. 2*

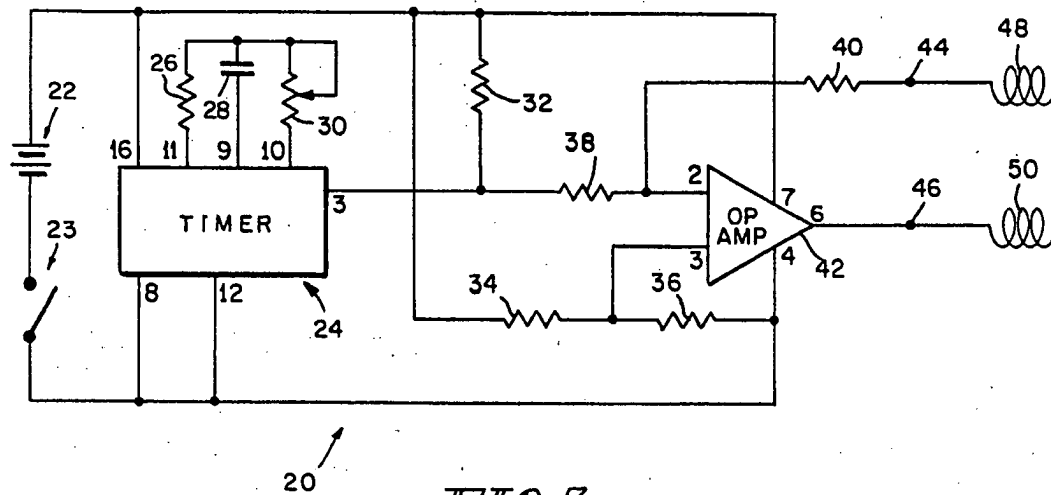


FIG 3

## METHOD AND APPARATUS FOR REGENERATING NERVES

This invention relates to a method and apparatus for causing nerves to regenerate, particularly, nerves in the central nervous system of mammals.

Injury to the spinal cord or central nervous system can be one of the most devastating and disabling injuries possible. Depending upon the severity of the injury, paralysis of varying degrees can result. Paraplegia and quadriplegia often result from severe injury to the spinal cord. The resulting effect on the sufferer, be it man or animal, is severe. The sufferer can be reduced to a state of near immobility or worse. For humans, the mental trauma induced by such severe physical disability can be even more devastating than the physical disability itself.

Heretofore, it has been long thought that once damaged, the nerves of the central nervous system in mammals do not regenerate and cannot be caused to regenerate within the environment of the central nervous system. Any regeneration of injured nerves in the central nervous system of mammals has been found to occur, if at all, only within a very short period immediately after the injury occurs. After this short period expires, such nerves have not been found to regenerate.

This is in marked contrast to nerves outside the central nervous system in mammals, i.e., nerves in the peripheral nervous system and even to nerves in the central nervous system of lower order vertebrates, not to mention invertebrates. Nerves in the peripheral nervous system of mammals are known to regenerate spontaneously. Further, past studies have shown that the regeneration of nerves in the peripheral nervous system of mammals can be stimulated by the application of electrical fields. Similar past studies have also shown that regeneration of nerves in the central nervous system of lower order vertebrates, such as lampreys, can be stimulated by the application of electrical fields. Past studies have also shown that if nerves from a spinal cord of a mammal are taken out of the central nervous system environment and placed in a peripheral nervous system environment, the nerves will in fact regenerate. In one such study, it was found that axons from central nervous system neurones would regenerate into peripheral nervous system grafts. (P. Richardson, V. McGuinness, and A. Aguaso, "Axons From CNS Neurones Regenerate into PNS Grafts," *Nature*, 284, 264-286)

More recently, it was disclosed that a steady state DC electrical field would stimulate axons to grow into the glial scar in guinea pigs having partially severed spinal cords. (R. Borgens, A. Blight, D. Murphy and L. Stewart, "Transected Dorsal Column Axons Within the Guinea Pig Spinal Cord Regenerate in the Presence of an Applied Electrical Field," *Journal of Comparative Neurology*, 250: 168-180 (1986). However, although such an electrical field stimulates axon growth in one direction, i.e., axons facing the cathode, it not only will retard axon growth in the opposite direction, i.e., anodal facing axons, but will actually cause anodal facing axons to reabsorb into the bodies of their nerve cells.

In a study involving embryonic spinal neurites (axons) of frogs, it was found that while the application of a steady state DC electrical field would stimulate neurite growth toward the cathode almost immediately, reabsorption of anodal facing neurites would begin to occur only after a period of time elapsed. (C. McCaig,

"Spinal Neurite Reabsorption and Regrowth In Vitro Depend on the Polarity of an Applied Electric Field," *Development* 100, 31" (May, 1987). This study found that the rate of reabsorption began slowly and increased as time elapsed. The maximal phase of retraction (reabsorption) of anodal facing neurites was found to take place over a twenty minute period roughly one hour after the onset of reabsorption. This study also disclosed that when the polarity of the electrical field was reversed, reabsorption of the previously anodal facing neurites was halted and neurite growth was stimulated in that direction. In contrast, growth of the previously cathodal facing neurites was halted and these neurites began to reabsorb after a period of time. The study concluded by stating that reabsorption induced by an electrical field was found to be most severe within one to one and one half hours after the field was applied whereas regeneration was promoted optimally within twenty minutes after the electrical field was reversed. The study then postulated that if the results reflected what might happen in vivo, then an optimal regime for electrical stimulation across a lesion might be to alternate the polarity of the electrical field every half hour to one hour, ensuring that the electric field was applied early on before excessive die-back of axons occurred.

Even with the results of these most recent studies, conventional thinking remains that nerves in the central nervous system of mammals will not regenerate within the central nervous system environment and cannot be caused to regenerate. Applicants, however, have found that by applying an oscillating electrical field to the central nervous system of a mammal, the nerves in the central nervous system can be stimulated to regenerate within the central nervous system. By oscillating electrical field it is meant that a DC electrical field is imposed in one direction for a period of time to promote growth in one direction and the polarity of the field then reversed before die back of the oppositely facing axons begins or becomes significant.

It is an object of this invention to stimulate nerves in the central nervous system of mammals to regenerate within the central nervous system.

In accordance with this invention, the nerves in the central nervous system of a mammal are stimulated to regenerate by applying an oscillating electrical field to the central nervous system. The oscillating electrical field is illustratively a constant current DC field the polarity of which is reversed after a predetermined time. The predetermined time is set to be less than the die-back period of anodal facing axons.

Additional features and advantages of the invention will become apparent to those skilled in the art upon consideration of the following detailed description of a preferred embodiment, exemplifying the best mode of carrying out the invention as presently perceived. The detailed description particularly refers to the accompanying figures in which:

FIG. 1 is a graph which shows the effect of an applied steady DC field over time on the growth of cathodal and anodal facing axons;

FIG. 2 is a graph which shows the effect of an applied oscillating field over time on the growth of cathodal and anodal facing axons; and

FIG. 3 is a schematic of a circuit for generating an oscillation electrical field for stimulating nerve regeneration.

In accordance with this invention, nerves in the spinal cord of a mammal are stimulated to regenerate

within the spinal cord by the application of an oscillating electrical field to the spinal cord. The oscillating electrical field is a constant current DC stimulus which is first applied in one direction for a predetermined period of time and then applied in the opposite direction for the predetermined period of time. In other words, the polarity of the constant current DC stimulus is reversed after each predetermined period of time. The predetermined period of time, which is the time period of one half-cycle of the oscillating electrical field, is selected to be less than the die back period of anodal facing axons but long enough to stimulate growth of cathodal facing axons. Applicants believe that in mammals, this predetermined period will need to be at least thirty seconds to stimulate growth of cathodal facing axons. This predetermined period will be termed the "polarity reversal period" of the oscillating electrical field.

When the spinal cord of a mammal is injured, connections between nerves in the spinal cord are broken. Conventionally, the injured portion of the spinal cord is termed a lesion. Such lesions block the flow of nerve impulses for the nerve tracts affected by the lesion with resulting impairment to both sensory and motor function.

To restore the lost sensory and motor functions, the affected motor and sensory axons of the injured nerves must regenerate, that is, grow back. Unfortunately, this has not been found to occur in the spinal cord of mammals. Applicants, however, have found that by applying a DC electrical field across a lesion in the spinal cord of mammals, axon growth can be promoted and the axons will grow back around the lesion. Since the spinal cord is rarely severed completely when injured, the axons need not actually grow across the lesion but can circumnavigate the lesion through remaining spinal cord parenchyma. However, such findings have met with widespread disbelief. Conventional thinking remains that the nerves in the spinal cord of mammals will not regenerate within the spinal cord and cannot be caused to do so.

Although it has been known that axon growth can be promoted in the peripheral nervous system of mammals and in the central nervous system of lower order vertebrates by the application of a steady DC electrical field, only those axons facing the cathode (negative pole) are stimulated to grow. Axons facing the anode (positive pole) not only are not stimulated to grow, but actually reabsorb into the bodies of the nerve cells ("die back"), after a period of time. As discussed previously, McCaig has found that significant die back or reabsorption of anodal facing axons begins to occur about one hour after the DC electrical field is applied. The period of time which elapses from when a DC electrical field is first applied to when significant reabsorption or die back of the anodal facing axons begins will be termed the "die back period." McCaig's experiments were conducted using embryonic spinal cord cells of frogs.

In order to "repair" an injured spinal cord, regeneration of both the ascending and descending nerve tracks must be promoted. Thus, axons growth in both directions, i.e., rostrally and caudally, must be stimulated to "repair" an injured spinal cord. Applicants have found that applying an oscillating electrical field across a lesion in the spinal cord of a mammal will stimulate axon growth in both directions, i.e., caudally and rostrally. That is, growth of caudally facing axons will be promoted as will growth of rostrally facing axons.

FIGS. 1 and 2 show the affects on axon growth by an applied steady state DC electrical field (FIG. 1) and by an applied oscillating electrical field (FIG. 2). Referring to FIG. 1, a nerve cell 10 is shown at the left-hand side of FIG. 1 having a cell body or soma 12 from which an axon 14 extends upwardly and an axon 16 extends downwardly. At time 0, a constant current DC stimulus is applied to the nerve cell 10 such that axon 14 will be extending toward the cathode or negative pole of a DC stimulus signal and axon 16 will be extending toward the anode or positive pole of the DC stimulus. Axon 14 begins to grow almost immediately. However, after a period of time, i.e., the "die back period" ( $D_T$ ), significantly reabsorption of axon 16 into the cell body 12 begins and eventually axon 16 is completely reabsorbed into cell body 12. At the right hand of FIG. 1 nerve cell 10 is shown wherein axon 14 has grown substantially longer but axon 16 has been reabsorbed into cell body 12.

In FIG. 2, the same reference numbers will be used to identify the elements of FIG. 2 which correspond to elements of FIG. 1. Nerve cell 10 is shown at the left-hand side of FIG. 2 having a cell body 12, an upwardly extending axon 14 and a downwardly extending axon 16. At time 0, a constant current DC stimulus is applied to nerve cell 10 such that axon 14 is extending toward the cathode and axon 16 is extending toward the anode of the DC stimulus. After a predetermined period of time, the polarity of the DC stimulus is reversed. Axon 14 will now be extending toward the anode and axon 16 will be extending toward the cathode of the DC stimulus. The predetermined period of time is selected to be less than the die back period ( $D_T$ ) of the anodal facing axon. As has been discussed, significant die back of anodal facing axons begins to occur about one hour after the DC stimulus is applied. Therefore, the predetermined period should not exceed one hour. As shown in FIG. 2, this oscillating field stimulates growth of the axons facing both direction. This is due to the fact that growth of cathodal facing axons is stimulated almost immediately after the DC stimulus is applied but die back of the anodal facing axons does not become significant until after the die back period elapses. Since the polarity of the DC stimulus is switched before the die back period elapses, growth of axons in both directions is stimulated with the result that axons 14, 16 of nerve cell 12 both grow significantly longer as shown at the right-hand side of FIG. 2.

FIG. 3 is a schematic of a circuit for generating an oscillating field for application to the spinal cord of a mammal to stimulate nerve regeneration. Generator 20 includes a six volt battery 22, a power switch 23, a time 24, 6.2M resistor 26, 0.047  $\mu$ F capacitor 28, 2M potentiometer 30, 1M resistors 32, 34, 36, 15K resistor 38, 1K resistor 40, and low power operational amplifier 42. Illustratively, timer 24 is a 14-stage ripple counter and oscillator chip such as a CD4060BE and low power operational amplifier 42 is an ICL7611 low power CMOS operational amplifier, both of which are manufactured by RCA. Battery 22 illustratively comprises two series connected three volt lithium dioxide battery cells such as DL2025 battery cells manufactured by Duracell.

The positive terminal of battery 22 is coupled to the V+ terminal (pin 16) of the 14-stage ripple counter and oscillator chip which is timer 24 and to the V+ terminal (pin 7) of operational amplifier 42. Resistor 26, capacitor 28 and potentiometer 30 are used to set the fre-

quency of the oscillator of the 14-stage ripple counter and oscillator chip. One terminal of resistor 26 is coupled to the clock input (pin 11) of timer 24 and its other terminal is coupled to a first terminal of capacitor 28 and to a first terminal of potentiometer 30. The first terminal of potentiometer 30 is also coupled to the wiper terminal of potentiometer 30. A second terminal of capacitor 26 is coupled to a first frequency set output (pin 9) of timer 24 and a second terminal of potentiometer 30 is coupled to a second frequency set output (pin 10) of timer 24. The V- terminal (pin 8) of timer 24 is coupled to a first terminal of switch 23. A second terminal of switch 23 is coupled to the negative terminal of battery 22. A reset input (pin 12) of timer 24 is also coupled to the first terminal of switch 23 as is the V- terminal (pin 4) of operational amplifier 42.

An output (pin 3) of timer 24 is coupled through resistor 32 to the positive terminal of battery 22 and through resistor 38 to the negative input (pin 2) of operational amplifier 42. The positive input (pin 3) of operational amplifier 42 is coupled through resistor 34 to the positive terminal of battery 22 and through resistor 36 to the first terminal of switch 23. The negative input (pin 2) of operational amplifier 42 is coupled through resistor 40 to an output terminal 44. The output (pin 6) of operational amplifier 42 is coupled to an output terminal 46.

Output terminal 44 of stimulator 20 is coupled to an electrode 48 and output terminal 46 is coupled to an electrode 50. Illustratively, electrodes 48, 50 comprise silastic insulated platinum electrodes.

When power switch 23 is closed, generator 20 generates an oscillating electrical field at output terminals 44, 46. That is, generator 20 generates a constant current DC stimulus the polarity of which is reversed periodically after the expiration of a predetermined period of time determined by timer 24. Output terminals 44, 46 will thus alternately comprise cathode and anode terminals, respectively, of generator 20 depending upon the polarity of the DC stimulus.

The predetermined period of time determined by timer 24 is set by the frequency of the oscillator in the 14-stage ripple counter and oscillator chip which is timer 24. Potentiometer 30 is used to set the frequency of the oscillator in the 14-stage ripple counter and oscillator chip. The output of this oscillator can then be divided by up to 14 binary stages by the 14-stage ripple counter and oscillator chip to achieve very low frequency oscillations. If the frequency of this oscillator is illustratively set to 4.5 Hz and divided by these 14 binary stages, a frequency of one cycle per hour at the output (pin 3) of the 14-stage ripple counter and oscillator chip (timer 24) is produced which causes generator 20 to reverse polarity every thirty minutes. Applicants have found that a polarity reversal every fifteen minutes is effective to stimulate nerve regeneration in dogs, although a longer period would be more effective though possibly less safe. In guinea pig studies, applicants have used a polarity reversal period of thirty minutes to effectively stimulate nerve regeneration.

The output of timer 24 is taken from the appropriate binary stage of the 14-stage ripple counter and oscillator chip, which, in the embodiment shown, is the output of the fourteenth stage (pin 3) and is a square wave oscillator between 0 VDC and 6 VDC (railed at the supply voltage) with a frequency determined as described above. This square wave is applied to the inverting input (pin 2) of operational amplifier 42. Resistors 34,

36, illustratively being equal, set up a 3 VDC reference voltage at the positive input (pin 3) of operational amplifier 42. Therefore, depending on whether the output of timer 24 is high or low, there will be a net +3 VDC or -3 VDC at the inverting input of operational amplifier 42 which drives current through electrodes 48, 50.

The magnitude of the current sourced by generator 20 is determined by the value  $R_c$  in the equation:

$$I = \frac{3V}{R_c}$$

where  $R_c$  is resistor 38 and the 3V is determined by the net voltage differential between the inverting and non-inverting inputs of operational amplifier 42.

If generator 20 is to source currents less than 100  $\mu A$ , the quiescent current of operational amplifier 42 is set to 1  $\mu A$  by strapping its pin 8 to +V. If generator 20 is to source more than 100  $\mu A$ , the quiescent current of operational amplifier 42 is set to 10  $\mu A$  by letting pin 8 float.

The current sourced by generator 20 is selected to provide sufficient field strength in the section of the spinal cord in which nerve regeneration is to be stimulated. Applicants have found that a field strength of 200  $\mu V/mm$  in the spinal cord will stimulate regeneration. The current needed to achieve this field strength is determined, such as by experiment, by the geometry of the animal in which generator 20 is used. Applicants have found that a current of 20  $\mu A$  will provide a sufficient field strength to stimulate nerve regeneration in the spinal cords of guinea pigs whereas a current of about 200  $\mu A$  is needed to provide sufficient field strength to stimulate nerve regeneration in the spinal cords of dogs weighing approximately twenty to thirty pounds.

Power switch 23 is used to disconnect power to generator 20 until generator 20 is ready to be used. Timer 24 draws approximately 45  $\mu A$  and to prevent this power drain from occurring prematurely, power switch 23 is used to keep power disconnected until generator 20 is put in use. Preferably, generator 20 is packaged in a sealed package since it will preferably be implanted in a subject. To permit power switch 20 to be actuated when it is enclosed within such a sealed package, power switch 23 is illustratively a normally closed magnetic reed switch. A magnet is then detachably affixed to the packaged generator 20 to hold switch 23 open until generator 20 is ready for use. The magnet is then removed permitting the magnetic reed switch which is power switch 23 to close. Alternatively, power switch 23 could be a latching magnetic reed switch. Power switch 23 could also be a sealed mechanical switch which can be actuated from outside the sealed package of generator 20. Finally, power switch 23 could be dispensed with altogether and either the positive or negative terminal of battery 22 left disconnected until generator 20 is ready for use. At that time, the terminal would be connected. This would, of course, require that the package in which generator 20 is placed be left open to some extent and sealed up at this time.

Electrodes 48, 50 are implanted on opposite sides of a lesion in the spinal cord, respectively. Applicants have found that it is sufficient to implant electrodes 48, 50 in a laminectomy adjacent the spinal cord but not actually in the spinal cord. Further, in studies involving the application of a steady state DC electrical field, applicants have found that moving the anode from within the laminectomy to a site on the muscle dorsal to the same

area results in only about a ten percent drop in field strength as does the converse of moving the cathode to a more superficial position while leaving the anode in the laminectomy. Further, uniform field homogeneity can be achieved by locating the electrodes anywhere on the midline of the spinal cord, including locating both electrodes on the same side of the lesion but spaced apart, although locating the electrodes on opposite sides of the lesion is preferred.

Applicants have also found that the field strength within the spinal cord at the site of the lesion depends upon the location of the current delivery electrodes. The convergence of current to an electrode produces high current density and hence higher field strength near each electrode. The closer one electrode is to the lesion site, the less critical is the placement on the other to maintain high field strengths. However, as a current delivery electrode approaches the lesion, current direction becomes less uniform. At a lesion exactly half-way between two electrodes placed on the midline, the current will all be oriented along the long axis of the subject animal. As one of the electrodes is moved closer to the lesion, there will be a larger vertical (dorsal-ventral) component of the current at the lesion (assuming that the electrodes remain a few millimeters dorsal to the target tissue). As a compromise between uniform current direction and maximum field strength, applicants have chosen to position the electrodes two vertebral segments on either side of the lesion in their spinal cord studies. In the guinea pig studies applicants have conducted, it appears that the critical distance to be within one convergence zone of an electrode (that area in which the current convergence to the electrode so dominates the field strength that the position of the other electrode is relatively inconsequential) is approximately 1 cm. Therefore, by placing one electrode within 1 cm of the lesion, the position of the other becomes relatively inconsequential and becomes a matter of convenience. It should be noted, however, that the electrodes can be located further from the lesion. If they are, the field strength of the electrical field at the lesion for a given magnitude of current will be reduced. Therefore, the magnitude of the current would have to be increased to yield the same electrical field strength at the lesion.

In addition to promoting axon growth in both directions, use of an oscillating electrical field also reduces the production of electrode products which alter the pH of the environment surrounding the electrode. Applicants have found that after twenty-four hours of application of a constant 35  $\mu$ A of a steady state DC electrical field, the pH at the cathode well (environment surrounding the cathode electrode) was 9.8 and the pH at the anode well was 3.4. After 48 hours, the pH at the anode well was 2.4. In contrast, after 60 hours of application of an oscillating electrical field where the polarity of the DC stimulus was reversed every forty-five minutes, the largest pH change at either well was 0.4 pH units.

Although the invention has been described in detail with reference to certain preferred embodiments and specific examples, variations and modifications exist within the scope and spirit of the invention as described and as defined in the following claims.

What is claimed is:

1. A method for stimulating nerves in the central nervous system of a mammal to regenerate within the central nervous system comprising the step of applying

an oscillating electrical field to the spinal cord wherein the electrical field's polarity reversal period is less than about sixty minutes which is less than a die back period of anodally facing axons in the central nervous system and more than about thirty seconds which is long enough to stimulate growth of cathodally facing axons in the central nervous system.

2. A method for stimulating axon growth in the spinal cord of a mammal to stimulate nerve regeneration comprising the step of applying an oscillating electrical field across a lesion in the spinal cord wherein the oscillating electrical field's polarity reversal period is long enough to stimulate growth of cathodally facing axons in the spinal cord but is less than a die back period of anodally facing axons in the spinal cord.

3. The method of claim 2 wherein the polarity reversal period of the oscillating electrical field is in the range of thirty seconds to sixty minutes.

4. A method for stimulating nerves in the central nervous system of a mammal to regenerate within the central nervous system comprising the steps of implanting electrodes on opposite sides of a lesion, generating an oscillating electrical field that has a polarity reversal period in the range of about thirty seconds to about sixty minutes, and applying the oscillating electrical to the electrodes to apply the oscillating electrical field to the central nervous system.

5. A method for stimulating nerves in the central nervous system of a mammal to regenerate, said nerves having nerve cells with caudally extending axons and rostrally extending axons, comprising the steps of applying a constant current DC stimulus to the central nervous system and reversing the polarity of the DC stimulus after a predetermined period of time which is in the range of about thirty seconds to about sixty minutes.

6. The method of claim 5 wherein the polarity of the DC stimulus is reversed each time the predetermined period of time elapses.

7. An apparatus for stimulating nerves in the central nervous system of a mammal to regenerate within the central nervous system, comprising means for generating an oscillating electrical field which as a polarity reversal period long enough to stimulate growth of cathodally facing axons of the nerves to be stimulated but less than a die back period of anodally facing axons of the nerves to be stimulated and means for coupling an output of the generating means to the central nervous system.

8. The apparatus of claim 7 wherein the output of the generating means has first and second oppositely polarized output terminals and the means for coupling the output of the generating means to the central nervous system comprises first and second electrodes coupled respectively to the first and second outputs of the generating means.

9. The apparatus of claim 8 wherein the means for generating the oscillating electrical field generates the oscillating electrical field with a polarity reversal period in the range of thirty seconds to sixty minutes.

10. An apparatus for stimulating axon growth of the nerve cells in the spinal cord of mammals to stimulate regeneration of the nerve cells in the spinal cord, comprising means for generating a constant current DC stimulus, the generating means having first and second oppositely polarized output terminals wherein one output terminal comprises a cathode and the other output terminal comprises an anode of the generating means,



means for coupling the first and second output terminals to the spinal cord on opposite sides of a lesion, and means for reversing the polarity of the DC stimulus each time a predetermined period of time elapses, the predetermined time period being in the range of about thirty seconds to sixty minutes, and wherein each time the polarity of the DC stimulus is reversed the output terminal which comprised the cathode before the polarity reversal comprises the anode after the reversal and

the output terminal which comprised the anode before the polarity reversal comprises the cathode after the polarity reversal.

11. The apparatus of claim 10 wherein the means for coupling the first and second output terminals to the spinal cord comprises first and second electrodes coupled respectively to the first and second output terminals.

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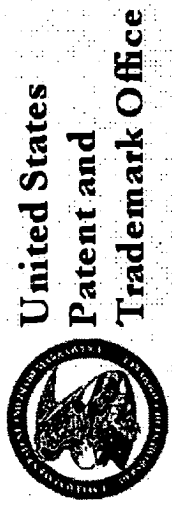
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4,919,140	\$930.00	\$0.00	05/10/93	07/258,142	04/24/90	10/14/88	04	NO	3220-18158

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4,919,140	\$2,100.00	\$0.00	10/24/97	07/258,142	04/24/90	10/14/88	08	NO	3220-18158

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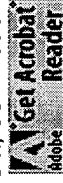
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Patent Number:	4919140	Application Number:	07258142
Issue Date:	04/24/1990	Filing Date:	10/14/1988
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Patent Number:	4919140	Application Number:	07258142
Issue Date:	04/24/1990	Filing Date:	10/14/1988
Title: METHOD AND APPARATUS FOR REGENERATING NERVES			
Status:	4th, 8th and 12th year fees paid		Entity: Large
Window Opens:	N/A	Surcharge Date: N/A	Expiration: N/A
Fee Amt Due:	Window not open	Surchg Amt Due: Window not open	Total Amt Due: Window not open
Fee Code:			
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Most recent events (up to 7):	10/23/2001 Payment of Maintenance Fee, 12th Year, Large Entity. 10/24/1997 Payment of Maintenance Fee, 8th Year, Large Entity. 06/16/1997 Payor Number Assigned. 06/16/1997 Payer Number De-assigned. 05/20/1993 Payor Number Assigned. 05/12/1993 Pat Hldr no Longer Claims Small Ent Stat as Nonprofit Org.. 05/10/1993 Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---		
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## Comparison of Medical Device to Claims of US Patent No. 4,919,140

1. A method for stimulating nerves in the central nervous system of a mammal to regenerate within the central nervous system comprising the step of :	The Medical Device and method undergoing approval is for stimulating nerves in the central nervous system of a human mammal to regenerate within the spinal cord a part of the central nervous system. (Exhibit A page 6, paragraph 2 ("A-6, ¶ 2")).
applying an oscillating electrical field to the spinal cord	The Medical Device applies an oscillating electric field to the spinal chord (A-3, ¶ 1) via implantation of three black electrodes on one side of a spinal cord lesion and three white electrodes on the opposite side of the lesion (A-2, ¶ 2) with the polarity of all of the black electrodes being the same and the polarity of all of the white electrodes being the same with the polarities of the black and white electrodes being switched simultaneously. (A-14, ¶ 2), (A-17, ¶ 2).
wherein the electrical field's polarity reversal period is less than about sixty minutes which is less than a die back period of anodally facing axons in the central nervous system	The polarity switches every fifteen minutes (A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2) in the Medical Device which is far less than sixty minutes and the die back period of anodally facing axons in the central nervous system. (see U.S. Patent No. 4,919,140, column3, lines 42-56 ("140,C. 3, ll. 42-56"), ('140, C.4, ll. 32-37)).
and more than about thirty seconds which is long enough to stimulate growth of cathodally facing axons in the central nervous system.	The polarity switches every fifteen minutes (A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2) in the Medical Device which is far more than thirty seconds and is long enough to stimulate growth of cathodally facing axons in the central nervous system. (see '140, C. 4, ll. 7-12 and 39-44).

2. A method for stimulating axon growth in the spinal cord of a mammal to stimulate nerve regeneration comprising the step of	The Medical Device and method undergoing approval is for stimulating axon growth in the spinal cord of a human mammal to stimulate nerve regeneration (A-6, ¶ 2) comprising the step of
applying an oscillating electrical field across a lesion in the spinal cord	The Medical Device applies an oscillating electric field (A-3, ¶ 1) across a lesion in the spinal chord via implantation of three black electrodes on one side of a spinal cord lesion and three white electrodes on the opposite side of the lesion (A-2, ¶ 2) with the polarity of all of the black electrodes being the same and the polarity of all of the white electrodes being the same with the polarities of the black and white electrodes being switched simultaneously (A-3, ¶ 1)
wherein the oscillating electrical field's polarity reversal period is long enough to stimulate growth of cathodally facing axons in the spinal cord but is less than a die back period of anodally facing axons in the spinal cord.	The polarity switches every fifteen minutes (A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2) in the Medical Device which is far more than the period required to stimulate growth of cathodally facing axons and less than the die back period of anodally facing axons in the spinal cord. (see '140, C. 3, ll. 42-56, C.4, ll. 7-12 and 32-44).

3. The method of claim 2	See above
wherein the polarity reversal period of the oscillating electrical field is in the range of thirty seconds to sixty minutes	The Medical Device has a polarity reversal period of oscillating electric field of fifteen minutes (A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2) which is in the range of thirty seconds to sixty minutes



4. A method for stimulating nerves in the central nervous system of a mammal to regenerate within the central nervous system comprising the steps of	The Medical Device and method undergoing approval is for stimulating axon growth in the spinal cord of a human mammal to stimulate nerve regeneration (A-6, ¶ 2).
implanting electrodes on opposite sides of a lesion,	The electrodes of the Medical Device are implanted on opposite sides of a lesion (A-2, ¶ 2) (A-6, ¶ 3) (A-14, ¶ 2).
generating an oscillating electrical field that has a polarity reversal period in the range of about thirty seconds to about sixty minutes,	The Medical Device generates an oscillating electrical field that reverses polarity every fifteen minutes (A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2).
and applying the oscillating electrical to the electrodes to apply the oscillating electrical field to the central nervous system.	The Medical Device applies an oscillating electrical field to the electrodes (A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2) which when implanted applies an oscillating electrical field to the central nervous system (A-3, ¶ 1) (A-14, ¶ 2).

5. A method for stimulating nerves in the central nervous system of a mammal to regenerate, said nerves having nerve cells with caudally extending axons and rostrally extending axons, comprising the steps of	The Medical Device and method undergoing approval is for stimulating axon growth in the spinal cord of a human mammal to stimulate nerve regeneration (A-6, ¶ 2) which nerves have nerve cells with caudally and rostrally extending axons.
applying a constant current DC stimulus to the central nervous system and	The Medical Device applies a constant current DC stimulus of 600micro amps (A-3, ¶ 1) which provides a 600 microvolts per millimeter electrical field to the spinal cord of the central nervous system (A-14, ¶ 2) (A-16, ¶ 6).
reversing the polarity of the DC stimulus after a predetermined period of time which is in the range of about thirty seconds to about sixty minutes.	The Medical Device reverses the polarity of the DC stimulus every fifteen minutes(A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2) which is within the range of thirty seconds to sixty minutes.

6. The method of claim 5	See above.
wherein the polarity of the DC stimulus is reversed each time the predetermined period of time elapses.	The Medical Device reverses the polarity of the DC stimulus every fifteen minutes (A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2).

7. An apparatus for stimulating nerves in the central nervous system of a mammal to regenerate within the central nervous system, comprising	The Medical Device is for stimulating nerves in the central nervous system of a human mammal to regenerate within the spinal cord a part of the central nervous system. (A-6, ¶ 2).
means for generating an oscillating electrical field which has a polarity reversal period long enough to stimulate growth of cathodally facing axons of the nerves to be stimulated but less than a die back period of anodally facing axons of the nerves to be stimulated and	The Medical Device has an oscillating field stimulator including a battery (see '104, C. 4, l. 49-C. 6, l. 6 and Fig.3) (A-6, ¶ 5) (A-18) timer (see '104, C. 4, l. 49-C. 6, l. 6 and Fig.3) ) (A-7, ¶ 2) (A-9, #28) (A-10, all) (A-13) (A-14, IC1) (A-18) comprising a 14 stage ripple counter (see C. 5, l. 56) (A-7, ¶ 2) (A-10, #20) (A-14, IC1) (A-18, ¶ 1), an oscillator set circuit (see '104, C. 4, l. 64-C.5, l. 16, C. 5, ll. 41-60 and Fig 3) (A-15), and switch (A-14, IC2)(A-18, ¶ 1) configured to generate an oscillating electrical field that reverses polarity every fifteen minutes which is far less than the die back period of anodally facing axons in the central nervous system. (see '140, C. 3, ll. 42-56), ('140, C.4, ll. 32-37) and far more than long enough to stimulate growth of cathodally facing axons in the central nervous system. (see '140, C. 4, ll. 7-12 and 39-44).
means for coupling an output of the generating means to the central nervous system.	The Medical Device has electrodes electrically coupled to the output of the oscillating field stimulator that are configured for suturing adjacent the spine above and below a lesion. (A-2, ¶ 2) (A-3, ¶ 1) (A-6, ¶ 3) (A-7, ¶ 2) (A-13) (A-14, ¶ 2) (A-15)

8. The apparatus of claim 7	See above
wherein the output of the generating means has first and second oppositely polarized output terminals and	The Medical Device includes an oscillating field stimulator having first and second oppositely polarized output terminals to which two leads are coupled . (A-2, ¶ 2) (A-3, ¶ 1) (A-6, ¶ 3) (A-7, ¶ 2) (A-13) (A-14, ¶ 2) (A-15).
the means for coupling the output of the generating means to the central nervous system comprises first and second electrodes coupled respectively to the first and second outputs of the generating means.	The Medical Device has electrodes electrically coupled to the output of the oscillating field stimulator that are configured for suturing adjacent the spine above and below a lesion. (A-2, ¶ 2) (A-3, ¶ 1) (A-6, ¶ 3) (A-7, ¶ 2) (A-13) (A-14, ¶ 2) (A-15).
9. The apparatus of claim 8	See above.
wherein the means for generating the oscillating electrical field generates the oscillating electrical field with a polarity reversal period in the range of thirty seconds to sixty minutes.	The Medical Device reverses the polarity of the oscillating electrical field every fifteen minutes(A-3, ¶ 1) (A-6, ¶ 4) (A-7, ¶ 2) (A-14, ¶ 2) which is within the range of thirty seconds to sixty minutes.

10. An apparatus for stimulating axon growth of the nerve cells in the spinal cord of mammals to stimulate regeneration of the nerve cells in the spinal cord, comprising	The Medical Device is for stimulating axon growth of the nerve cells in the spinal cord of a human mammal to stimulate nerve regeneration of the nerve cells in the spinal cord (A-6, ¶ 2).
means for generating a constant current DC stimulus, the generating means having first and second oppositely polarized output terminals wherein one output terminal comprises a cathode and the other output terminal comprises an anode of the generating means,	The Medical Device includes an oscillating field stimulator having stimulator including a battery (see '104, C. 4, l. 49-C. 6, l. 6 and Fig.3) (A-6, ¶ 5) (A-18) and first and second oppositely polarized output terminals to which two leads are coupled one acting as a cathode and the other acting as an anode. (A-2, ¶ 2) (A-3, ¶ 1) (A-6, ¶ 3) (A-7, ¶ 2) (A-13) (A-14, ¶ 2) (A-15).
means for coupling the first and second output terminals to the spinal cord on opposite sides of a lesion,	The Medical Device has electrodes electrically coupled to the output of the oscillating field stimulator that are configured for suturing adjacent the spine above and below a lesion. (A-2, ¶ 2) (A-3, ¶ 1) (A-6, ¶ 3) (A-7, ¶ 2) (A-13) (A-14, ¶ 2) (A-15).
and means for reversing the polarity of the DC stimulus each time a predetermined period of time elapses, the predetermined time period being in the range of about thirty seconds to sixty minutes, and	The Medical Device has an oscillating field stimulator including a timer (see '104, C. 4, l. 49-C. 6, l. 6 and Fig.3) ) (A-7, ¶ 2) (A-9, #28) (A-10, all) (A-13) (A-14, IC1) (A-18) comprising a 14 stage ripple counter (see C. 5, l. 56) (A-7, ¶ 2) (A-10, #20) (A-14, IC1) (A-18, ¶ 1), an oscillator set circuit (see '104, C. 4, l. 64-C.5, l. 16, C. 5, ll. 41-60 and Fig 3) (A-15) and switch (A-14, IC2)(A-18, ¶ 1) configured to generate a DC stimulus that reverses polarity every fifteen minutes which is within the range of about thirty seconds to sixty minutes.
wherein each time the polarity of the DC stimulus is reversed the output terminal which comprised the cathode before the polarity reversal comprises the anode after the reversal and the output terminal which comprised the anode before the polarity reversal comprises the cathode after the polarity reversal.	The Medical Device is configured so that each time the polarity of the DC stimulus is reversed the output terminal which comprised the cathode before the polarity reversal comprises the anode after the reversal and the output terminal which comprised the anode before the polarity reversal comprises the cathode after the polarity reversal. (A-3, ¶ 1) (A-6, ¶ 3) (A-7, ¶ 2) (A-13) (A-14, ¶ 2) (A-15).

11. The apparatus of claim 10	See above
wherein the means for coupling the first and second output terminals to the spinal cord comprises first and second electrodes coupled respectively to the first and second output terminals.	The Medical Device has a first set and second set of electrodes electrically coupled to the output terminals of the oscillating field stimulator that are configured for suturing adjacent the spine above and below a lesion. (A-2, ¶ 2) (A-3, ¶ 1) (A-6, ¶ 3) (A-7, ¶ 2) (A-13) (A-14, ¶ 2) (A-15)

**Statement of the Relevant Dates and Information pursuant to 35 U.S.C. §156(g)  
in order to enable the Secretary of Health and Human Services  
to Determine the Applicable regulatory Review Period**

The relevant dates and information pursuant to 35 U.S.C. §156(g) ) in order to enable the Secretary of Health and Human Services to Determine the Applicable regulatory review Period are as follows:

Documentation of Review and Approval documents were submitted to the IUPUI and Clarian Institutional Review Boards & Subcommittee Reviews (the "IRB") for a "Pilot Study For Treating the Severely Injured Spinal Cord With An Extraspinal Oscillating Field Stimulator" (The "Pilot Study") on June 15, 1999.

Approval of the Pilot Study by the IRB was granted December 9, 1999.

Approval for a Feasibility Study was granted by the FDA on August 30, 2000.

The date on which the Humanitarian Use Device (HUD) designation request #05-0159 was submitted for Investigation Device Exemption Number pursuant to 21 CFR section 812.20 was October 21, 2005.

The effective date of the Investigational Device Exemption (IDE) was August 31, 2006. The IDE Number was IDE G000195.

The date on which the Humanitarian Device Exemption Designation was filed was February 16, 2007.

**A brief description of the significant activities  
undertaken by Purdue Research Foundation and its  
licensees prior to and during the applicable  
regulatory period with respect to the Medical Device**

**A) Pre-regulatory Non-human trials for proof of concept and determination of safety for documentary support for IDE request as indicated in HHS Publication FDA 96-4149.**

1990	First clinical trials utilizing dogs initiated to test effectiveness of original packaging design begun with device not including all of the safety features to be present on human device to aid in establishing major health effects of the medical device.
October 19, 1992	Publication on first clinical trials utilizing dogs with device not including all of the safety features to be present on human device submitted.
January 21, 1993	Publication on first clinical trials with dogs utilizing dogs with device not including all of the safety features to be present on human device accepted for publication following requested revisions.
1994	Second clinical trials on dogs begun with device including higher electrical fields than first study and safety features to be present on human device to aid in establishing major health effects of the Medical Device. Medical Device was identical to that later implanted in humans for human trials.
1998	Completed second clinical trial on dogs using device identical to that implanted in humans during human trials.
November 7, 1999	Published results of second clinical trial on dogs using device identical to that implanted in humans during human trials.



**B) Efforts to Obtain Regulatory Approval**

June 15, 1999	Documentation of Review and Approval submitted to IUPUI and Clarian Institutional Review Boards & Subcommittee Reviews for Study Number 8808.12 ("Pilot Study for Treating Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator." (See Appendix A).
July 6, 1999	FDA IDE manual obtained.
July 8, 1999	Preparation of IDE request started by Borgens.
circa July 1999	FDA contacted by phone to obtain information regarding IDE process.
August 17, 1999	Documentation of Review and Approval for Pilot Study for Treating Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator entered in minutes of IRB. (See Appendix A).
August 30, 1999	Institutional Review Board (IRB) of Indiana University School of Medicine, Department of Surgery, Department of Neurological Surgery provisionally approved clinical human trials contingent upon receipt of IDE approval. (See Appendix B).
October 5, 1999	Certification sent to IRB that all investigators had signed a letter of agreement regarding Pilot Study for Treating Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator. (See Appendix C).
December 9, 1999	Final approval of IRB received for Pilot Study for Treating Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator. (See Appendix A).
May 2, 2000	First Patient enrolled in Pilot Study for Treating Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator.
August 30, 2000	An application to conduct a ten person feasibility study (IDE#G000195) at Indiana University by primary investigator

("Sponsor") Scott A. Shapiro MD was approved by the FDA.  
Clinical Investigation begun.

March 29, 2001 Medical device implanted in B\_W01 pursuant to Feasibility Study for Testing the Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator (Ref. #00-164). Remainder of Patient Demographic information included in Table 5 appearing on page 18 of the HDE request (attached as Appendix D) For each patient, neurological assessments were made at four time periods, prior to implant and six weeks, six months and twelve months post implant.

January 7, 2004 Completion of first ten patients' involvement in Feasibility Study for Testing the Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator (Ref. #00-164).

August 27, 2004 Sponsor received approval from FDA to enroll an additional ten patients in the Feasibility Study for Testing the Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator (Ref. #00-164).

October 21, 2005 Humanitarian Use Device (HUD) designation request #05-0159 submitted for Investigation Device Exemption Number pursuant to 21 CFR section 812.20.

November 1, 2005 FDA Questions

December 9, 2005 FDA Questions

February 14, 2006 CKI acquires Andara Life Science, Inc.

February 20, 2006 Additional Data/Response to Questions Submitted

March 8, 2006 Additional Data/Response to Questions Submitted

March 22, 2006 Additional Data/Response to Questions Submitted

May 5, 2006 Additional Data/Response to Questions Submitted

June 15, 2006 E-mail message from Dr. Sarah Linde-Feucht of the FDA requesting clarification as to intended use of the Medical Device

July 26, 2006 Additional Data/Response to Questions Submitted

August 31, 2006	HUD Designation Granted by FDA as IDE G000195 pursuant to Fed. FDCA section 520(m). (See Appendix E).
December 22, 2006	Human clinical investigation of Andara OFS device under IDE G00195 completed
February 16, 2007	Humanitarian Device Exemption submittal. (See Appendix F).
May 9, 2007	1st Set of Questions from FDA
July 10, 2007	Response to 1st Questions
December 7, 2007	2nd Set of Questions from FDA
February 28, 2008	Meeting with FDA to clarify appropriate manner for responding to second set of Questions generated December 7, 2007
March 14, 2008	Response to 2nd Questions
June 6, 2008	FDA Questions & determination to use Clinical Panel
August 8, 2008	Package went out to Clinician Panel

## INTERDEPARTMENTAL COMMUNICATION

Research and Sponsored Programs  
Indiana University - Purdue University Indianapolis

DATE: December 9, 1999

TO: Scott A. Shapiro  
Neurosurgery  
c/o Sandy Kay EH 139  
IUPUI

FROM: Sara Ellis *je*  
Research Compliance Coordinator, UN 618

SUBJECT: Final Approval

Study Number: 9908-12 Pilot Study for Treating the Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator  
Sponsor: Special State (Indiana) - Appropriation House Bill 1244

The study listed above has received final approval from the Institutional Review Board. **IMPORTANT NOTICE** The Institutional Review Board (IRB) now requires that the consent statement given to subjects have the IRB approval stamp on the last page. As the principal investigator of this study, you assume the following reporting responsibilities:

1. **CONTINUING REVIEW** - A status report must be filed with the Board. The Research Compliance staff will generate these reports for your completion; however, you must request and complete these forms if the study is terminated for any reason in the interim. This study is approved from **December 9, 1999, to December 9, 2000.**
2. **STUDY AMENDMENTS** - Investigators are required to report on these forms ANY changes to the research study including protocol design, dosages, timing or type of test performed, population of the study, and informed consent statement. An amendment form is attached for your future use in submitting study amendments for committee review.
3. **ADVERSE EVENTS** - If this is a medical study, all side effects or adverse reactions which are serious and unexpected must be reported immediately to the Board as they occur (see attached requirements).
4. **UPDATED INVESTIGATIONAL BROCHURES, PROGRESS REPORTS and FINAL REPORTS** - If this is an investigational drug or device study, updated clinical investigational brochures must be submitted as they occur (see attached requirements). Three copies of progress or final reports must be provided to the Board with the investigator's written assessment of the report, briefly summarizing any changes and their significance to the study.
5. **ADVERTISEMENTS** - If you will be advertising to recruit study participants for a drug or device study regulated under FDA requirements, i.e., investigational drugs or devices will be used, and the advertisement was not submitted to the Board at the time your study was reviewed, a copy of the information contained in the advertisement and the mode of its communication must be submitted to the reviewing board as an amendment to the study. These advertisements must be reviewed and approved by the Board **PRIOR** to their use.
6. **LEAVING THE UNIVERSITY** - If the principal investigator leaves the Institution, the Board must be notified as to the disposition of **EACH** study.

PLEASE REFER TO THE ASSIGNED STUDY NUMBER AND THE EXACT TITLE IN ANY FUTURE CORRESPONDENCE WITH OUR OFFICE. All documentation related to this study must be neatly typed and must also be maintained in your files for audit purposes for at least three years after termination of the research. If you have any questions, please call Research and Sponsored Programs at 274-8289.

Enclosures:	<input checked="" type="checkbox"/> Documentation of Review and Approval	<input checked="" type="checkbox"/> Report of Updated Clinical Investigational Brochures
	<input checked="" type="checkbox"/> Expedited Review Checklist	<input checked="" type="checkbox"/> Report of Adverse Reactions
	<input checked="" type="checkbox"/> Amendment Form	<input type="checkbox"/> Copy of Assurance Letter
	<input checked="" type="checkbox"/> Informed Consent Statement	

DHHS Multiple Project Assurance #M1167, IRB No. 01 available at <http://www.iupui.edu/it/rspinfo/assurance.html>

## APPENDIX A

## IUPUI AND CLARIAN INSTITUTIONAL REVIEW BOARDS &amp; SUBCOMMITTEE REVIEWS

## DOCUMENTATION OF REVIEW AND APPROVAL

STUDY NUMBER: 0000.121

1. PRINCIPAL INVESTIGATOR Scott A. Shapiro, MD DEPARTMENT Neurosurgery  
 (Must have faculty/staff status or faculty sponsor)  
 BUILDING/RM. NO EM 139 TELEPHONE 274-2784  
 E-MAIL ADDRESS skkay@iupui.edu

2. PROJECT TITLE: Pilot Study for Treating the Severely Injured Spinal Cord with an Extraspinal Oscillating Field Stimulator

3. CHECK TYPE OF REVIEW: Expedited (Please send original plus 2 copies--3 total)  
☒ Full (Please see Page 2, Item 4 for number of copies needed)

4. CHECK IRB: ☒ Biomedical Behavioral or Social Sciences

5. FUNDING AGENCY (include pending): Special State (Indiana) PI ON GRANT: Shapiro

6. GRANT TITLE (if different from project title): Appropriation House Bill 1244  
Indiana University: Spinal Cord Injury/Research

7. SPONSOR'S PROTOCOL #/GRANT # (unless pending): 27-881-01 Period: July 1, 1999 -  
 from to

8. RESEARCH TO INCLUDE: ☒ Minors Prisoners  
 (Special Subject Populations) ☒ Pregnant Women Economically or Educationally Disadvantaged  
☒ Mentally Disabled

9. RESEARCH SUBMISSION ☒ Informed Consent, dated                      ☒ Protocol, dated                       
 INCLUDES: ☒ Drug Brochure, dated                      ☒ Advertisement, dated                       
☒ Other (Description)                      dated                     

10. The principal investigator must assure the Board that all procedures performed under the project will be conducted in strict accordance with those federal regulations, University and Clarian Health Partners policies which govern research involving human subjects. Any deviation from the project (e.g., change in principal investigator, research methodology, subject recruitment procedures, etc.) will be submitted to the Board in the form of an amendment for IRB approval prior to implementation.

NOTE: This form and any additional material requested by the Board will not be processed unless neatly typed and legible, properly prepared, and signed personally by the principal investigator.

June 15, 1999  
 Date

[Signature]  
 Principal Investigator (Signature)

\*\*\*\*\*FOR OFFICE USE ONLY\*\*\*\*\*

This protocol and informed consent statement for use of human subjects in research has been reviewed and approved by the Indiana University-Purdue University Indianapolis Institutional Review Board or the Clarian Institutional Review Board for a maximum of a one year period beyond the final approval date unless otherwise indicated as follows:                     

[Signature]  
 Authorized IRB Signature

12/9/99  
 IRB Approval Date

Recorded in the Minutes of:
AUG 17 1999

5:00PM  
 RECEIVED  
 22 JUL 99 10:10  
 DHHS Multiple Project Assurance #M1167, IRB No. 01  
 RECEIVED



INDIANA UNIVERSITY

SCHOOL OF MEDICINE

DEPARTMENT OF SURGERY  
Department of Neurological Surgery  
Wishard Memorial Hospital  
1001 West Tenth Street  
East Outpatient Building, Room 323  
Indianapolis, Indiana 46202  
(317) 630-7625 FAX (317) 630-8721

8/30/99

Richard Borgens, Ph.D.

Dear Richard,

The IRB has been provisionally approved; however, it hinges obviously on getting the IDE#. I have to make a few corrections to what I submitted that are all basically nothing more than typographical errors. I have to tighten up the statistics area a little bit, but other than that there will be no problems in getting it approved. The main problem is we all know will be the IDE#.

Your Friend,

A handwritten signature in black ink, appearing to read "Scott A. Shapiro".

Scott A. Shapiro, M.D.  
Professor of Neurosurgery  
Department of Neurosurgery

SAS/pam

APPENDIX B



INDIANA UNIVERSITY

SCHOOL OF MEDICINE

DEPARTMENT OF SURGERY  
Department of Neurological Surgery  
Wishard Memorial Hospital  
1001 West Tenth Street  
East Outpatient Building, Room 323  
Indianapolis, Indiana 46202  
(317) 630-7625 FAX (317) 630-8721

10/5/99

**CERTIFICATION:**

All investigators have signed the accompanying letter of agreement, these are the only investigators in the Study and no new investigators will be added to the investigation until they sign a letter of agreement.

IRB Chairman at Indiana University Medical Center: Conrad Johnston, MD

**APPENDIX C**  
**C-1**



INDIANA UNIVERSITY

SCHOOL OF MEDICINE

DEPARTMENT OF SURGERY  
Department of Neurological Surgery  
Wishard Memorial Hospital  
1001 West Tenth Street  
East Outpatient Building, Room 323  
Indianapolis, Indiana 46202  
(317) 630-7625 FAX (317) 630-8721

175

10/5/99

To Whom It May Concern:

We the investigators of the study titled "Pilot Study for treating Severe Human Spinal Cord Injury with an Extraspinal Oscillating Field Stimulator" agree to obtain a written informed consent prior to placing the patient on the study. We also agree to abide precisely by the protocol. No additional investigator shall be added to the study without first signing this agreement. We also agree to abide by all local IRB regulations and all federal regulations in running this study using the oscillating field stimulator.

Sincerely,

Scott A. Shapiro, M.D., FACS

Paul Nelson, MD, FACS

Richard Borgens, PhD.

Robert Pascuzzi, MD



reliability of the classification. Table 5 lists patient demographics. Patient gender and race are presented in Table 6.

*Table 5: Patient demographics.*

Patient	Sex	Age	Injury Date	Pre-Op ASIA Exam Date	Days to Pre-Op ASIA	Implant Date	Days to OFS	Explant Date	Level of Injury	Cause	Int. Fix.
B W01	M	20	3/17/2001	3/28/2001	11	3/29/2001	12	7/10/2001	T1-T2	SMB	Yes
D V02	F	41	3/24/2001	4/10/2001	17	4/10/2001	17	8/3/2001	C6-C7	MVA	Yes
D P05	M	23	4/22/2001	5/3/2001	11	5/4/2001	12	8/17/2001	T5-T6	ATVA	Yes
SES	F	17	5/19/2001	5/24/2001	5	6/1/2001	13	9/14/2001	T9	ATVA	Yes
MLC03	M	27	10/7/2001	10/22/2001	15	10/23/2001	16	2/5/2002	T4-T5	MVA	Yes
RLZ07	M	21	1/19/2002	1/31/2002	12	2/5/2002	17	5/21/2002	C5	Diving	Yes
D C06	M	43	8/26/2002	9/5/2002	10	9/6/2002	11	12/20/2002	C6-C7	Fall	Yes
L L08	M	27	9/12/2002	9/26/2002	14	9/27/2002	15	1/10/2003	C5	MVA	Yes
D E04	M	23	10/24/2002	11/5/2002	12	11/8/2002	15	2/21/2003	T10	Fall	Yes
BAI09	M	22	11/17/2002	11/22/2002	5	11/26/2002	9	3/11/2003	T8-T9	MVA	No
JGR10	M	18	12/26/2002	1/8/2003	13	1/10/2003	15	4/25/2003	C5	Viol.	No
BJM11	F	31	12/10/2005	12/17/2005	7	12/20/2005	10	4/11/2006	C6-C7	MVA	Yes
NAG12	M	19	1/23/2006	2/6/2006	14	2/7/2006	15	5/30/2006	C6-C7	MVA	Yes
NJH13	F	23	3/1/2006	3/16/2006	15	3/16/2006	15	7/1/2006	C6-C7	MVA	Yes
Average		25.4			11.5		13.7				

SMB: Snowmobile; ATVA: All terrain vehicle accident; MVA: Motor vehicle accident; Viol.: Violence

*Table 6: Patient gender and race.*

Gender	Number of Participants	White	Black	American Indian or Alaskan Native	Asian or Pacific Islander	Other
Female	4*	3	1	0	0	0
Male	10	8	2	0	0	0
Total	14*	79%	21%	0	0	0

\* Compassionate use patient

## E. NEUROLOGICAL ASSESSMENTS

To assess efficacy of the Andara™ OFS™ System, neurological assessments were made using the American Spinal Injury Association (ASIA) Standard Neurological Classification of Spinal Cord Injury published in 1992. Neurological assessments were made at four time periods: baseline (prior to implant), 6 weeks, 6 months, and



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

## Public Health Service

Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

August 31, 2006

Richard Stephenson  
Regulatory Affairs Consultant  
28 Tower Hills Drive  
Redds Spring, Missouri 65737

Re: Humanitarian use device designation request # 05-0159

Dear Mr. Stephenson:

Reference is made to your humanitarian use device (HUD) request on behalf of Andara Life Science, Inc., a wholly owned subsidiary of Cyberkinetics Neurotechnology, Inc., dated October 21, 2005, of the extraspinal oscillating field stimulator (OFS) for the "treatment of acute, complete spinal cord injuries." Please also refer to our letters dated November 1 and December 9, 2005, and to your submissions dated February 20, March 8 and 22, May 5, and July 26, 2006. Please also refer to the meeting with this Office on February 24, 2006.

Pursuant to section 520(m) of the Federal Food, Drug, and Cosmetic Act your request for humanitarian use device designation of the extraspinal oscillating field stimulator is granted for *treatment of acute, complete spinal cord injuries*.

You should know that an approved HUD indication may be modified again during the process of approving your application for a Humanitarian Device Exemption, which is the next step to obtaining marketing approval. During that step, the safety and efficacy data you provide will be reviewed by the FDA Center for Devices and Radiological Health. We recommend that you review this website for HDE guidance:  
<http://www.fda.gov/cdrh/ode/guidance/1381.html>.

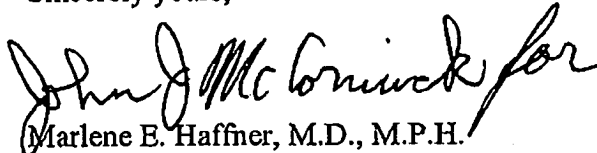
We would also like to let you know that there are mechanisms in place to get unapproved medical devices to patients in certain circumstances through FDA's Expanded Access Program. You can get more information about this program through the FDA website at [www.fda.gov/cdrh/devadvice/ide/early.shtml](http://www.fda.gov/cdrh/devadvice/ide/early.shtml).

Humanitarian use device designation request # 05-0159

2

Please refer to this letter as official notification of designation. Congratulations on obtaining a HUD designation.

Sincerely yours,

A handwritten signature in cursive script, reading "John J. McGinnis for". The signature is written in black ink and is positioned above the typed name and title.

Marlene E. Haffner, M.D., M.P.H.  
Rear Admiral, United States Public Health Service  
Director, Office of Orphan Products Development

February 16, 2007

Document Mail Center (HFZ-401)  
Office of Device Evaluation  
Center for Devices and Radiological Health  
9200 Corporate Blvd.  
Rockville, MD 20850

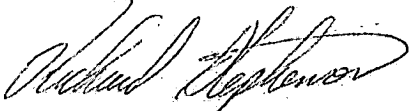
Dear Sir or Madam:

Cyberkinetics Neurotechnology Systems, Inc. received FDA approval of its humanitarian use device (HUD) request # 05-0159 by letter dated August 31, 2006. The approval designates the extraspinal oscillating field stimulator (OFS) for the treatment of acute, complete spinal cord injuries to be a humanitarian use device. Cyberkinetics plans to make the medical device available under the trade name of Andara™ OFS™ System. This is the original Humanitarian Device Exemption application for the Andara™ OFS™ System.

As a result of failures on the part of the laboratory conducting some of the biocompatibility studies to meet previously agreed upon timeframes, a telephone conversation was held with FDA Reviewer Kristen Bowsher, PhD on February 9, 2007. We explained the delays caused by the laboratory, the materials in contact with tissue, and requested that we be allowed to submit the HDE application without all of the biocompatibility test results present. She agreed with the understanding that Cyberkinetics will amend the HDE application with the balance of the test results around the middle of March. As agreed with Dr. Bowsher this HDE application does not contain two biocompatibility reports but it does contain the test protocols for the two tests.

Cyberkinetics looks forward to working with FDA during the review of this HDE application. Any questions or need for clarification should be directed to [RichardStephenson1@hotmail.com](mailto:RichardStephenson1@hotmail.com). Alternatively I can be contacted at either (417) 338-1099 or at cell phone number (979) 285-5397.

Sincerely,



Richard Stephenson  
Regulatory Affairs Consultant

**APPENDIX F**

**F-1**

## **GENERAL INFORMATION**

**SUBMISSION TYPE:** Original HDE

**DEVICE TRADE NAME:** Andara™ OFS™ System

**DEVICE GENERIC NAME:** Spinal Nerve Stimulator

### **SPONSOR**

Cyberkinetics Neurotechnology Systems, Inc.

100 Foxborough Boulevard

Suite 240

Foxborough, MA 020305

Tim R. Surgenor, President and CEO

Phone: 508-549-9981

### **HDE APPLICATION PREPARED BY**

Richard Stephenson

28 Tower Hills Drive

Reeds Spring, MO 65737

Phone: 417-338-1099

Email: RichardStephenson1@hotmail.com

**Statement That In The Opinion Of The Applicant The Patent Is Eligible  
For The Extension And A Statement As To The Length Of Extension Claimed,  
Including How The Length Of Extension Was Determined**

**1. Reasons for which an interim Extension Is Available**

In the opinion of Purdue Research Foundation ("PRF"), U.S. Patent No. 4,919,140 ("the OFS Patent") is eligible for an interim patent term extension pursuant to 35 U.S.C. 156(d). While PRF is only petitioning currently for a one year interim extension until the earlier of October 14, 2009 or sixty days following regulatory approval, PRF ultimately believes that it will become entitled to petition for an extension of the OFS Patent that may exceed 1773 days (see below for the proper calculation) as a result of the continuing pre-market regulatory review of the Medical Device, assuming the HDE request is treated as a Premarket Approval Request that is exempt from the effectiveness requirements of Section 515 so that the date of filing of the same can be treated as the initial submission of an application "with respect to the device under section 515." The preliminary calculation of the extension term to which the OFS Patent is entitled does not include periods in which non-human clinical studies were performed to establish the major health effects and scientific basis for the utilization of the Medical Device to treat spinal cord injuries or the period of submissions seeking IRB approvals for Human Pilot Studies or Human Pilot Studies performed prior to FDA approval of the IDE on August 30, 2000, which periods may increase the number of days that the term of the OFS Patent should be extended. The reasons the applicant believes that it is entitled to an interim extension of the OFS Patent for at least one year or until sixty days after regulatory review is completed are as follows:

- (a) The term of the OFS Patent has not expired before this application is submitted.
- (b) The term of the Patent has never been extended.
- (c) The application for interim patent term extension is submitted by an authorized agent of the record owner of the OFS Patent.
- (d) The Medical Device has been subject to a regulatory review period before its commercial marketing or use as evident from Exhibits E and F.

(e) The first commercial marketing of Andara™ OFS™ System will follow the approval of request for approval for the commercial marketing or use of the Medical Device.

(f) Applicant reasonably believes that Regulatory Approval of a Humanitarian Device Exemption will be received on the Medical Device.

## **2. Calculation**

Applicant believes that the OFS patent is eligible for a one year interim patent term extension and will, upon approval of the HDE application be eligible for a longer extension which cannot be finally determined until the regulatory review is completed. Without relinquishing its rights to subsequently request a longer period of extension for regulatory review activity predating this application for interim extension, the applicant has made a determination that the OFS patent is at least eligible for an extension of 1773 days. This period might be increased if the time for performing clinical trials on animals is included (began 1990). This period might also be increased if the period between obtaining IRB approval which was granted on December 9, 1999 (an additional 234 days would be added to the number of days indicated in (a) below) and the beginning of conducting human trials pursuant to the IRB and FDA approved Feasibility Study which was granted on August 30, 2000, as adjusted to account for any period in which the applicant did not act diligently is included in the calculation (which would extend the calculated extension period to October 14, 2013). The below calculation in no way should be interpreted as relinquishing Applicant's right to seek a five year extension of the term of the patent following completion of regulatory review. This determination was made by:

(a) Determining the number of days in the period beginning on the date of clinical investigation on humans involving the device was begun and ending on the date an application was initially submitted with respect to the device under the Federal Food Drug, and Cosmetic Act = 2362 days (between August 30, 2000 and February 16, 2007).

(b) Determining the number of days in the period beginning on the date of the application was initially submitted with respect to the medical device under the Federal Food, Drug, and Cosmetic Act, and ending on the date of the filing of this application for

interim extension (in view of the fact that approval of the application has yet to be received) = 592 days (February 16, 2007 to September 29, 2008).

(c) Adding the results of paragraphs (a) and (b) = 2954 days (2362+592).

(d) Determining the number of days in the periods of paragraphs (a) and (b) which were on and before the date on which the patent issued = 0 days.

(e) Determining the number of days in the periods of paragraphs (a) and (b) in which applicant did not act with due diligence = 0 days.

(f) Determining one half of the number of days remaining in the period defined in paragraph (a) after that period is reduced in accordance with paragraphs (d) and (e) = 1181 days (2362days/2).

(g) Subtracting the number of days determined in paragraphs (d) (e) and (f) from the number of days determined in paragraph (c) = at least 1773 days (2954-0-0-1181).

(h) Adding the number of days determined in paragraph (g) to the original term of the patent (October 14, 2008) as shortened by any terminal disclaimer = some time following August 22, 2013.

(i) Adding fourteen years to the date of approval of the application under the Federal Food, Drug, and Cosmetic Act = No earlier than September 29, 2022.

(j) Comparing the dates obtained in paragraphs (h) and (i) and selecting the earlier date = at least some time following August 22, 2013.

(k) Adding five years to the original expiration date of the OFS Patent (October 14, 2008) or earlier date set by terminal disclaimer = October 14, 2013.

(l) Comparing the dates obtained in paragraphs (j) and (k) and selecting the earlier date = some time following August 22, 2013 but no later than October 14, 2013.

Since regulatory approval has yet to be received for the Medical Device and because the OFS Patent would be eligible for a patent term extension until at least following August 22, 2013, if approval had been received on the date of filing this application for interim extension, in the opinion of the Applicant, the term of the OFS Patent should be interimly extended to the earlier of October 14, 2009 or sixty days following regulatory approval of the Medical Device, subject to further interim



extensions of up to one year if regulatory approval is not received sixty days prior to any interim extension granted to the OFS Patent.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re US Patent No. 4,919,140:	Borgens, et al.
Filed	October 14, 1988
Issue Date	April 24, 1990
Title	Method And Apparatus For Regenerating Nerves

Mail Stop Hatch-Waxman PTE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**Amendment and Supplement to Request for Interim Patent Term Extension**

Please consider this a submission of additional information requested by the United States Patent and Trademark Office pursuant to 35 U.S.C. 156. Applicant's attorney received a call from Mary Till of the United States Patent and Trademark Office on Thursday October 2, regarding the application for extension of US Patent No. 4,919, 140. Examiner Till indicated that, while the application implied that the Medical Device covered by the above named patent was undergoing regulatory approval under section 515 of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), that there was no express statement that approval was being pursued under that specific section of the act.

Applicant relies on 21 CFR § 814 for the proposition that a Humanitarian Device Exemption application is "an application . . . submitted with respect to the device under section 515 of the Federal Food, Drug, and Cosmetic Act" as set forth in 35 U.S.C. § 156 (g)(3)(B) and 37 C.F.R. § 1.777(c)(1). Subpart 814.1(a) of Title 21 of the C.F.R. states

that "This part implements section 515 of the act by providing procedures for the premarket approval of medical devices intended for human use." 21 C.F.R. § 814.1(a). As used in title 21 of the CFR, "the act" means the FDCA. 21 C.F.R. § 814.3(a). Subpart 814.3(m) of Title 21 states that "*HDE* means a premarket approval application submitted pursuant to this subpart seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the act as authorized by section 520(m)(2) of the act." 21 C.F.R. § 814.3(m). Subpart H of Part 814 including subparts 814.100-814.126 governs premarket approval under the Humanitarian Device Exemption.

Examiner Till also indicated that the Application for patent term extension did not include the HDE number assigned by the Food and Drug Administration for the HDE application submitted on the Medical Device.

Applicant is submitting herewith a scanned copy of a letter dated February 21, 2007 from Pauline Fogarty of the Food and Drug Administration, Division of General Restorative and Neurological Devices, Office of Device Evaluation and Center for Devices and Radiological Health acknowledging receipt of the humanitarian device exemption "ORIGINAL application and indicating that the application has been assigned the following unique document control number.

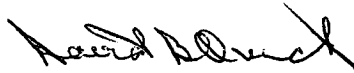
HDE Number: H070002  
Dated 16-Feb-2007  
Received 20-Feb-2007  
Device ANDARA OFS SYSTEM

Applicant is submitting herewith a Replacement page 2 of the Application that specifically recites that the approval sought by the HDE application is pursuant to

Section 515 of the FFDCA. Applicant is also submitting a replacement Exhibit E that sets forth the HDE number and date of receipt of the HDE application by the FDA. Additionally, applicant is submitting a Replacement page 4 to Exhibit F that identifies the date on which the FDA received the HDE application and the date on which the FDA acknowledged receipt of the application and provided applicant with the HDE number H070002. A newly submitted Appendix G to Exhibit E is a printout of a scanned copy of the FDA acknowledgement letter referred to above. Annotated copies of each replacement page submitted herewith indicating deletions by strike throughs and insertions by underlining are also provided. The replacement pages and annotated replacement pages are submitted in triplicate.

If there is any questions on this application, please contact the agent for the applicant, as noted above.

Respectfully Submitted



David B. Quick, Reg. No. 31,993  
Attorney for Applicant  
ICE MILLER LLP  
One American Square  
Suite 2900  
Indianapolis, IN 46282-0200

DBQ/sg

Encl: Replacement page 2 to Request for Interim Patent Term Extension (3x)  
Annotated Replacement page 2 (3x)  
Replacement Exhibit E (3x)  
Annotated Replacement Exhibit E (3x)  
Replacement page 4 to Exhibit F with New Appendix G (3x)  
Annotated Replacement page 4 to Exhibit F (3x)  
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context of the product currently undergoing review, Section (a)(3) and (a)(5) not being applicable to the request for interim extension.

(1) A complete identification of the medical device currently undergoing review (hereinafter, the "Medical Device") which is intended to be made available under the trade name of Andara™ OFS™ System, including its physical structure or characteristics is attached as **Exhibit A** which includes pages taken directly from the documents submitted to obtain regulatory approval.

(2) The regulatory review occurred in three stages. In Stage I clinical trials were conducted in compliance with IDE regulations in 21 CFR part 812, institutional review board regulations in 21 CFR part 56, and the informed consent regulations in 21 CFR part 50 pursuant to an IRB. In Stage II, the regulatory review comprised an Investigational Device Exemption Number Request under the Federal Food, Drug, and Cosmetic Act ("FFDCA") Section 520(g) (21 U.S.C. §360j(g)). In stage III, the regulatory review comprised a request for an Humanitarian Device Exemption under Investigational Device Exemption Number Request under the FFDCA Section 520(m) (21 U.S.C. §360j(m)) as a premarket approval application under Section 515 of the FFDCA.

(3) Not applicable to interim extension.

(4) Not applicable to requests for extension for medical devices.

(5) Not applicable to interim extension, however this application is being filed within the window of six months prior to the expiration of the term of the patent and fifteen days prior to the expiration of the term of the patent as prescribed in 35 U.S.C. §156(d)(5)(A). The patent term is to expire October 14, 2008, with the last day on which the Application for filing the interim extension request falling on September 30, 2008.

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Annotated (~~deletion~~, insertion)



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**Statement of the Relevant Dates and Information pursuant to 35 U.S.C. §156(g)  
in order to enable the Secretary of Health and Human Services  
to Determine the Applicable regulatory Review Period**

The relevant dates and information pursuant to 35 U.S.C. §156(g) ) in order to enable the Secretary of Health and Human Services to Determine the Applicable regulatory review Period are as follows: .

Documentation of Review and Approval documents were submitted to the IUPUI and Clarian Institutional Review Boards & Subcommittee Reviews (the "IRB") for a "Pilot Study For Treating the Severely Injured Spinal Cord With An Extraspinal Oscillating Field Stimulator" (The "Pilot Study") on June 15, 1999.

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Approval for a Feasibility Study was granted by the FDA on August 30, 2000.

The date on which the Humanitarian Use Device (HUD) designation request #05-0159 was submitted for Investigation Device Exemption Number pursuant to 21 CFR section 812.20 was October 21, 2005.

The effective date of the Investigational Device Exemption (IDE) was August 31, 2006. The IDE Number was IDE G000195.

The date on which the Humanitarian Device Exemption (HDE) Designation application under Sections 515 and 520(m) of the FDCA was filed was February 16, 2007.

The date on which the HDE application was received by the FDA Center of Device and Radiological Health, Office of Device Evaluation was February 20, 2007 with such application being assigned HDE number H070002.

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ANNOTATED (~~deletion~~, insertion)

Replacement EXHIBIT E

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ANNOTATED (~~deletion~~, insertion)

Replacement EXHIBIT E



August 31, 2006	HUD Designation Granted by FDA as IDE G000195 pursuant to Fed. FDCA section 520(m). (See Appendix E).
December 22, 2006	Human clinical investigation of Andara OFS device under IDE G00195 completed
February 16, 2007	Humanitarian Device Exemption ("HDE") submittal. (See Appendix F).
February 20, 2007	HDE received by FDA Center of Device and Radiological Health, Office of Device Evaluation, (see Appendix G).
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
Document Mail Center (HFZ-401)  
9200 Corporate Blvd.  
Rockville, Maryland 20850

February 21, 2007

TIM R. SURGENOR  
CYBERKINETICS, INC.  
100 FOXBORO BLVD. SUITE 240  
FOXBOROUGH, MA 02035

Dear TIM SURGENOR:

The Office of Device Evaluation, Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your humanitarian device exemption (HDE) ORIGINAL application and has assigned the following unique document control number to the application. Failure to reference this assigned number in future correspondence may result in processing delays.

HDE Number: H070002  
Dated: 16-FEB-2007  
Received: 20-FEB-2007  
Device: ANDARA OPS SYSTEM

In future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. ~~Under CDRH's eCopy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy.~~ For more information about the program, including the formatting requirements, please see [www.fda.gov/cdrh/elecsb.html](http://www.fda.gov/cdrh/elecsb.html).

Any questions concerning this submission should be directed to the undersigned at (240)276-3737. All future correspondence regarding this HDE should be identified with the HDE application number assigned above and should be submitted with the required number of copies to:

APPENDIX G

Document Mail Center (HFZ-401)  
Office of Device Evaluation  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, Maryland 20850

Sincerely yours,

*for Monique Wainwright*  
Pauline Fogarty  
Division of General, Restorative,  
and Neurological Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health



10-06-2008 07:25:23AM.JPG (600x574x16M jpeg)

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